From the Editor

Facts and ideas from anywhere

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THE PANDEMIC OF 1918 AND THE SEARCH FOR THE KILLER VIRUS

Dr. Jeremy Brown, a veteran emergency room physician, in his recent book entitled *Influenza: The Hundred-Year Hunt to Cure the Deadliest Disease in History*, explores the terrifying and complex history of the flu virus, from the origins of the Great Flu that killed 50

to 100 million people worldwide in 1918 to 1919 to its vexing annual return.¹ The pandemic (global outbreak, as opposed to epidemic, meaning local outbreak) killed about 675,000 Americans, 10 times as many as had died in combat during World War I. The war ended at the same time the flu was peaking. If a pandemic strain of influenza as deadly as the 1918 virus were to infect the USA today, >2 million people could die. Each year in the USA, the flu still kills from 35,000 to 50,000 people.

During the 100 years since the 1918 pandemic, we, of course, have learned an enormous amount about influenza. We now know its genetic code and how it mutates and makes us sick, and yet we still do not have an effective way to fight it. The present antiviral medications are relatively useless and the flu vaccine is a relatively poor defense. In good years, the vaccine is effective only half the time. The pandemic of 1918 killed more people than any other illness in recorded history! Because of its mystery, and its ability to mutate and spread, the flu is one of humankind's most dangerous foes.

In the pandemic of 1918, physicians tried a number of therapies, including bloodletting, laxatives (magnesia, calomel [mercury chloride]), aspirin, Friar's balsam (benzoin) or eucalyptus leaves, quinine, mustard plaster, codeine, phenolphthalein, castor oil, burning orange peels, diced onions, and poisonous gases, including chlorine gas. Not all physicians practiced like quacks during the pandemic. James B. Herrick (1861–1954), a prominent Chicago physician who was the first to describe sickle cell disease in 1910 and the nonfatal outcome of acute myocardial infarction in 1912, pleaded with physicians to stop using nearly all the medications in their arsenal, emphasizing that there was no evidence that any of them worked. He stressed that the condition was

self-limiting. Herrick recommended isolation, face masks, plenty of fluids, and lots of rest. Of the millions who typically get the flu virus each year, less than 1% die. Antibiotics, of course, are ineffective against the flu.

Dr. Brown emphasized that viruses have been on planet Earth for millions of years. How they developed initially is unknown. Brown described a virus as a box of chemicals without the structure of a cell. It cannot metabolize or replicate on its own. To reproduce it must invade living cells. Viruses infect bacteria, plants, reptiles, fish, birds, and mammals. They have intertwined with our evolution, and some have become incorporated into our genetic code. Nestled in the long strands of DNA are sequences that originated from ancient viruses. Their genetic code bonded with ours, making the virus a harmless part of us, freeloading off human cells to reproduce.

The word *virus* is a Latin word meaning poison, venom, or nauseous smell. These submicroscopic entities are 20 times smaller than bacteria. They contain a core of genetic material covered by a protein capsule, and they reproduce exclusively within living cells. The word *influenza* comes from the Italian word meaning influence. People once thought the influenza virus was due to a misalignment of the stars and planets.

Viruses have evolved to be quite different from the cells in our body. Unlike cells, viruses have no mitochondria, so they cannot make energy, and have no ribosomes, so they cannot build proteins. Viruses lack lysosomes that export waste and toxins. Viruses are simply an envelope containing a bundle of genes that exist only to make copies of themselves. They invade cells, reproduce, and then find a new victim to colonize. More than 2000 species of viruses have been identified, and the number keeps growing. Physicians are familiar with just a few of them: herpesvirus, rotavirus, rhinovirus, retrovirus, and orthomyxoviruses. The influenza virus comes from the orthomyxovirus. Three influenza viruses have been identified, and they go by A, B, and C. Only the A and B strains cause significant disease in humans, and it was the A strain that was responsible for the pandemic flu of 1918.

The influenza virus is shaped like a hollow ball and contains eight genes, made up of RNA (not DNA), which control the function of the virus. On its exterior are two important proteins: the spikey protein called hemagglutinin and a pitchfork-shaped protein on the surface called

neuraminidase. The hemagglutinin is inhaled into our lungs, latches onto the surface of our cells, and is absorbed into the cell; once there, the viral membrane dissolves, releasing the eight genes. These enter the nucleus of the invaded cell. From there the genes direct the cell to make millions of copies of the viral particle. These viral particles go back to the cell membrane and break free to invade other cells. The neuraminidase breaks the bond between the surface of the cell and the surface of the virus. The viral progeny is now free to be expelled (coughed or sneezed out) to invade another victim. The whole process takes a few hours and leaves behind destroyed respiratory cells.

During the process of reproduction, the flu virus may change in one or two ways and, as a result, new strains of the virus appear. As a result, the code of the progeny virus can differ from the parent virus and may result in slight modifications in the surface proteins of the virus. Since a person's immune system learns to identify a flu virus by the proteins on its surface, the modifications result in an unrecognizable flu virus, leading to a new strain. That is why people can become ill with the flu multiple times, being infected with a new virus each time.

Influenza A can develop new strains because of its capacity to infect different species (pig, bird, and horse). Sometimes two or more strains of the virus invade the same lung cell. There the gene from each strain can mix and produce a hybrid virus, containing the genetic material from both parents. Mammals get the flu in their lungs and birds get it in the gut. Infected bird droppings can contain billions of avian flu viruses, each ready to mingle with genetic material of other strains of influenza, including those that infect people. If a bird strain and a mammalian strain of influenza invade the same cell at the same time, their genes can mix to create an entirely new kind of flu virus that can turn deadly. That is apparently what happened in 1918 when birds contributed to parts of the influenza virus.

Although a single flu virus can produce millions of descendants as it takes over a cell, only a small number are actually able to reproduce. Nearly every genetic change that occurs results in a viral particle so damaged that it loses its ability to replicate. Given the millions of virus particles that generate when the flu invades a cell, however, even a success rate of 1% or 2% can result in thousands of flu viruses that can burst out of the cell and infect others.

It is unclear where the 1918 flu pandemic first appeared—Kansas, France, or China. Infection rates are much higher in the very young and the very old. In Europe today, the vaccine is given only to these two groups. In the pandemic of 1918, the curve was shaped like a “W” because those most affected were aged 21 to 29 years, a group usually considered to be the least likely to die from an infectious disease.

The search to discover the cause of the 1918 pandemic started before the pandemic had ended. A Japanese professor, T. Yamanouchi, studied 52 healthy physicians and nurses

after placing “an emulsion of the sputa” from influenza patients into the noses and throats of these volunteers. Some received this emulsion directly while others got it after filtering it through a fine mesh to capture all the bacteria. Both groups exhibited signs of influenza that led the Japanese researchers to affirm that no known bacteria could be the cause of the influenza pandemic. They also concluded that the disease spread by getting into the nose or throat of its victim, a feature of flu that we now take for granted but they barely recognized then.

In 1933, two British scientists working in London demonstrated that they could infect ferrets with samples obtained from patients' throats that were filtered to remove all bacteria, and they concluded that the pandemic was due to a virus infection. Another important advance in the same decade was the discovery that the influenza virus could be cultivated. It was injected into amniotic fluid of developing chick embryos. If it was possible to grow the virus, it also could be collected and killed and injected into healthy people.

In 1939, the newly invented electron microscope took a picture of a virus. For the first time in history, one could see the culprit. By the 1940s, two strains of influenza (A and B) were isolated and vaccines were developed. One of the scientists was Jonas Salk (1914–1995), who later developed the polio vaccine. After Francis Crick (1916–2004) and James Watson (1928–) discovered DNA in 1953, the building blocks of a virus were quickly identified. Virologists could then develop techniques to identify viruses and classify them based on their genetic components.

In 1994, Jeffery K. Taubenberger (1961–), head of the Department of Molecular Pathology at the Armed Forces Institute of Pathology and later at the National Institutes of Health, searched the original tissue samples at the institute and found 28 paraffin-embedded samples on 1 × 3 inch glass slides of lungs of the 1918 pandemic. He began the process of uncovering the genetic code of the 1918 virus. Like all flu viruses, the 1918 virus reaches peak replication 2 days after infection. After about 6 days, it stops multiplying and is not in the lungs. That meant that tissue from a patient who had contracted the 1918 virus and died from a secondary bacterial pneumonia several days later could not be used. Their tissue would not contain any virus particles; it would have been overrun with the bacterial infection that so often followed the viral infection. Taubenberger and his associates had to find samples from patients who had died within a week of initial symptoms. Finally, in one lung there was acute swelling of the walls of the tiny bronchi, something seen only in acute viral pneumonia. Taubenberger knew that most victims had died from complications of the influenza virus, but this particular victim had died from lung damage caused directly by the virus. He named this victim “1918 Case 1.” The sample belonged to Private Roscoe Vaughan, who had died on September 19 at Camp Jackson near Columbia, South Carolina. (My father, Stewart R. Roberts [1878–1941], was head of Camp Jackson during World War

I at that time.) After an autopsy, small specimens of his lungs were preserved in wax and then sent to the Armed Forces Institute of Pathology in Washington. They laid there for almost 80 years until Taubenberger and his colleagues discovered them in 1994. His lab was able to amplify the chains of some fragments of some genes that they found. One fragment was the gene that coded for influenza hemagglutinin. Taubenberger identified the genetic code that built the hemagglutinin protein on the surface of the 1918 influenza virus and compared it with the genes of other influenza viruses. This genetic detective work—routine today but groundbreaking 20+ years ago—settled a long debate as to the provenance of 1918. The virus appeared most closely related to a kind of swine flu, although later work would show this strain also had features in common with bird flu. The official name of the strain would be “Influenza A/South Carolina/1/18 (H1N1)” after the state from which the sample had originated. Today it would take about 2 weeks to sequence the whole genetic code of the 1918 virus, but in the 1990s it took 5 years for Taubenberger and his colleagues to identify the entire genome. Taubenberger identified four fragments of the hemagglutinin gene segment. The 1918 influenza virus was composed of various parts, each with a particular role. Some enabled the virus to enter the lung cells; others directed the cells to reproduce the virus and then release it, allowing it to infect more individuals. When the parts joined together, the virus became deadly.

They needed more samples to confirm their work. Enter a Swedish pathologist, Johan V. Hultin (1924–), who had come to the USA in 1949 as a visiting medical student. In his 20s, fascinated by influenza, he had taken advantage of a program at the medical school of Uppsala University that allowed its students to spend time abroad. Hultin went to the University of Iowa, where he intended to study the reaction of the body to influenza. In 1950, Hultin had a chance meeting with Roger Hale, a leading virologist who was visiting the university from the Brookhaven National Laboratory. Hale knew that the Swede was interested in flu research and told him that to advance the field he needed actual specimens of the 1918 virus. He suggested that Hultin go to Alaska to find a victim of the 1918 flu epidemic buried in the permafrost since 1918. Before coming to the University of Iowa, Hultin had worked in Fairbanks, Alaska, for a German paleontologist named Otto Geist (1888–1963), who gave him free board in return for help digging up mammoth tusks in the Arctic. Hultin now returned to Alaska where the bodies of those who had died in 1918 were buried in the permafrost. He had received a \$10,000 grant from his adopted university (about \$100,000 in today’s money) to go to Alaska and search for the victims. He met Geist in Alaska in 1951, and they traveled to Nome on the shore of the Bering Sea. Once there, they discovered that a flood had melted the permafrost. There was no soft tissue left, no lungs had survived, and there would be no virus to sample.

Hultin then hired a pilot to fly him further north to the village of Wales, where almost half of the 400 residents had died in the 1918 epidemic. There was a mass grave marked by a large cross that contained the remains of flu victims. He found, however, that the permafrost had not been so permanent. Hultin persuaded the pilot to fly him to Brevig Mission, a tiny village on the shore of the Bering Sea, where 72 of 80 residents died of flu in 1918. Brevig, however, did not have a landing strip, so he landed on the beach at a neighboring village, crossed the water on a whaleboat, and then walked 6 miles through the soggy tundra. In Brevig Mission, the permafrost was deep enough to preserve the bodies buried there. Hultin found three survivors of the 1918 epidemic and asked them to describe to the rest of the villagers what it had been like to live through the epidemic and to witness the deaths of almost everyone during one horrendous week in 1918. Hultin then explained to the villagers that obtaining specimens of the virus could create a vaccine and prevent another outbreak. With their support and that of the village council, he received permission to proceed. At first Hultin dug alone, but he was later joined by his faculty advisor, Otto Geist, the paleontologist. They exhumed five bodies, dissected them, and took small cubed samples from their preserved lung tissues. They wore only gloves and surgical masks for protection. The specimens were transported back to Iowa in dry ice, where Hultin injected mixtures of them into the amniotic fluid of growing chick embryos, the ideal medium for flu viruses. Disappointingly, the virus did not reproduce, so Hultin moved on to live animals—mice, guinea pigs, and ferrets. However, he was unable to infect any of them with the flu virus. The virus that had killed so many appeared no longer to be viable. It had been destroyed by time and the extremes of nature. The expedition was a failure.

Johan Hultin’s expedition thereafter remained forgotten, and he practiced pathology for the next 40 years and then retired. During his retirement, he read about Taubenberger’s work uncovering some of the genetic sequencing of the 1918 virus from the Armed Forces Institute of Pathology archives. Intrigued, Hultin wrote Taubenberger and told him about his 1950 expedition and its disappointing outcome. He offered to fly back to Brevig and try to recover the flu virus a second time. Hultin would finance the mission on his own. Now, 72 years old, he returned to Alaska to dig once again. The village elders at Brevig Mission not only gave him permission to exhume the bodies but also provided four young men to assist him. They dug with pick axes and shovels and eventually reached the depth of 7 feet. It was August 1997. After 3 days of digging by hand, Hultin found the body of an obese woman whom he named “Lucy.” The body fat had insulated her organs when the permafrost thawed. As a result, her lungs were intact. Hultin removed them and mailed the specimen to Taubenberger using three different carriers to minimize the risk that the packages would be lost. Within a week, the lab confirmed the presence of 1918 flu

particles in them. With more lung tissue than ever to work with, Taubenberger's lab could now rebuild the *entire* genetic code of the 1918 virus. Taubenberger announced the success of Johan Hultin's second expedition in August 1998. His lab became the sole custodian of samples of the 1918 flu virus. Because each sample might yield only part of the 1918 genetic code, still more were needed. When Taubenberger compared the genetic fingerprints across all of his samples, he found that the genetic material of the viruses was 99% identical, suggesting that only a single strain of the influenza was in circulation in the early stages of the 1918 outbreak, and that one specific antiviral drug or vaccine might be effective during the most lethal wave of any future flu epidemic. Finding the genetic code of the 1918 virus did not explain why it was so lethal, how the virus worked when it infected, or why it spread so quickly.

In 2005, researchers from four institutions announced that they had built several versions of the 1918 virus. The first was a complete working clone, with all eight of the original genes of the 1918 flu virus. It was capable of infecting test animals (and humans). The team also rebuilt versions of the virus that contained only one, three, or five of the original eight genes to use as controls. To test how lethal the virus was in mammals, the 1918 virus was sprayed into the noses of mice. Many died within 3 days. The lungs of these mice contained almost 40,000 times the amount of virus as the lungs of mice infected with the control version. The working eight-gene clone turned out to be at least 100 times deadlier than the five-gene version. It was clear that the cause of the virulence was the gene that coated hemagglutinin, the critical protein that sits on the surface of the virus and attaches to cells.

Thanks to Johan Hultin and Jeff Taubenberger, we now know the sequences of the genetic building blocks of the 1918 virus. We still do not know, however, why flu strains can affect some animals but not others; if the 1918 strain was an assortment of an existing flu virus that turned suddenly lethal or if that strain was a novel virus that appeared out of nowhere; or why the 1918 virus was particularly lethal in young adults (the group usually most resilient to infections). What has happened to the flu virus since the 1918 pandemic? Why did it become less lethal?

PLASTICS

Susan Freinkel produced a splendid book titled *Plastic: A Toxic Love Story*.² She began by listing during a 45-minute period one morning all items she touched that were made entirely or partially of plastic:

Alarm clock, mattress, heating pad, eyeglasses, toilet seat, toothbrush, toothpaste tube and cap, wallpaper, Corian counter, light switch, tablecloth, Cuisinart, electric teakettle, refrigerator handle, bag of frozen strawberries, scissor handle, yogurt containers, lid for can of honey, juice pitcher, milk bottle, seltzer bottle, lid of cinnamon jar, bread bag, cellophane wrapping around box of tea, packaging of tea bag, thermos, spatula handle, bottle of dish soap, bowl, cutting board, baggies, computer, fleece sweatshirt, sports bra, yoga

pants, sneakers, cat food container, cat food scooper, dog leash, Walkman, newspaper bag, stray packet of mayo on sidewalk, garbage can.

By the end of the day, she had touched 196 plastic items, recording each one only once. The next day, she recorded all nonplastic items she touched. By the end of that day, 102 items had been touched, giving a plastic/nonplastic ratio of nearly 2 to 1. The following was her list of nonplastic items:

Cotton sheets, wood floor, toilet paper, porcelain tap, strawberries, mango, granite-tile countertop, stainless steel spoon, stainless steel faucet, paper towel, cardboard egg carton, eggs, orange juice, aluminum pie plate, wool rug, glass butter dish, butter, cast-iron griddle, syrup bottle, wooden breadboard, bread, aluminum colander, ceramic plates, glasses, glass doorknob, cotton socks, wooden dining-room table, my dog's metal choke collar, dirt, leaves, twigs, sticks, and grass (and if I were not using a plastic bag, what my dog deposited amid those leaves, twigs, and grass).

All plastics, she indicated, have one thing in common: they are polymers, which in Greek stands for "many parts." They are made of long chains of thousands of atomic units called monomers, Greek for "one part," linked into giant molecules. All polymers are strong, durable, clear, flexible, and elastic. Chains crowded together make for a tough rigid plastic bottle, for example, and chains more widely spaced yield a more flexible bottle, a ketchup bottle.

Polymers appeared in 1907 when Belgian émigré Leo Baekeland (1863–1944) cooked up Bakelite, the first fully developed synthetic polymer, made entirely of molecules not found in nature. The dawn of plastics could be considered 1941, when, shortly after the bombing of Pearl Harbor, the director of the board responsible for provisioning the American military advocated the substitution, whenever possible, of plastics for aluminum, brass, and other strategic metals. World War II pulled polymer chemistry out of the lab and into real life. Many of the plastics that we know—polypropylene, nylon, acrylic, Styrofoam—got their first use during the war. By the end of the war, it was apparent that plastics could be used for nearly everything. After World War II, they began entering our homes, our cars, our clothes, our playthings, our workplaces, and even our bodies. They challenged traditional materials and won, taking the place of steel in cars, paper in glass and packaging, and wood in furniture. Ethylene gas, a byproduct of oil refineries, as a British chemist discovered in the early 1930s, could make polyethylene usable in packaging. Another byproduct, propylene, is now used in yogurt cups, microwaveable dishes, disposable diapers, and cars. Acrylonitrile could be made into acrylic fiber and into AstroTurf.

The amount of plastic the world consumes annually has steadily risen over the last 80 years, from almost nil in 1940 to >600 billion pounds yearly today. We became "plastic people" in the space of a single generation. In 1960, the average American consumed about 30 pounds of plastic each year; today, each of us consumes >300 pounds of plastic a year, which generates more than \$300 billion in sales. In

the 1940s, *cellophane* became the third most beautiful word in the English language, right after *mother* and *memory*. The early belief was that plastics would replace raw materials, preserving them. Synthetics could substitute for, or even precisely imitate, scarce and precious materials.

The polymer rapture, however, began to fade in the late 1960s, aided by a flood of products such as pink flamingos, vinyl siding, and Corfam shoes. Plastic's penchant for inexpensive imitation was seen as "being cheap." Today, few other materials we rely on carry such a negative association or stir such visceral disgust. Plastic is seen in some fundamental way to be essentially alien and unnatural. One reason is its endurance. Unlike traditional materials, plastic does not dissolve, rust, or break down, at least not in any meaningful timeframe. The plastic produced stays with us as litter, detritus on the ocean floor and in landfills. We humans could disappear from the Earth tomorrow, but many of the plastics we made will last for centuries.

Ms. Freinkel's book traces our relation with plastics from enraptured embrace to deep disenchantment. The author chose eight objects to tell the story of plastic: the comb, chair, Frisbee, intravenous bag, disposable lighter, grocery bag, soda bottle, and credit card. She explores efforts to develop more sustainable ways of producing and disposing of plastics. She does not discuss the plastic in cars, appliances, or electronics.

We have produced nearly as much plastic in the first decade of this millennium as we did in the entire 20th century. Plastics have invaded modern medicine extensively, as it has many other areas. Neonatology owes a huge debt to the advent of plastics. Polymers made organ transplantation possible. Willem Kolff (1911–2009) scrounged sheets of cellophane and other materials in Nazi-occupied Holland to produce his kidney dialysis machine. Today, plastic is in pacemakers, artificial hips and knees, in the housing components of imaging devices, and in bedpans, bandages, single-use gloves, and syringes. (They appeared in the 1950s but became indispensable in the wake of AIDS.) With plastics, hospitals could ship equipment that had to be laboriously sterilized in blister-packed disposables, something that improved in-house safety, significantly lowered costs, and made it possible for patients to be cared for at home. Medicine, however, is a small end-market, consuming less than 10% of all polymers produced in the USA—peanuts compared to packaging (33%), consumer products (20%), and building and construction (17%). Medicine is a strong recession-proof market and one that has provided the industry an enormous public relation value. Medicine has long been plastic's indisputable good news story, the showcase of polymers' benefit.

Plastics in medicine may also do harm. The same bags and tubes that deliver medicines and nourishment to those most vulnerable also deliver chemicals that can damage our health. Vinyl plastic, typically used in intravenous bags and tubing, contains a softening chemical. This chemical,

"phthalate," can mimic or block or suppress production of hormones. They potentially may make us more vulnerable to asthma, diabetes mellitus, obesity, heart disease, infertility, and attention deficit disorder. Some of these substances can damage even at minute concentrations.

Few objects speak to the medical impact of plastics as well as the plastic intravenous bag and its tubing. Carl W. Walter (1905–1992), a surgeon and clinical professor at Harvard Medical School, began studying the problems plaguing blood collection and storage in the late 1940s, following World War II. The whole idea of blood banking was still new. Walter established one of the first blood banks, locating it in an obscure basement room at Harvard to avoid arousing the ire of university trustees who considered it "unethical and immoral" to collect and use human blood. Blood banks in that era faced significant problems. Rubber tubing was used for the collection of the donor's blood, and it was stored in rubber-stoppered glass bottles, a process that often damaged the red cells and allowed bacteria and air bubbles to get in. Searching for a better system, Walter hit on the idea of using polyvinyl chloride, better known as PVC or vinyl, a unique polymer. Unlike other plastics, PVC has chlorine as one of its chief ingredients, a greenish gas derived from salt. To make PVC, the chlorine is mixed with hydrogen carbons to form the monomer vinyl chloride. The chloride base makes PVC chemically stable, fire resistant, waterproof, and cheap. It also makes PVC hazardous to manufacture and a nightmare to dispose of because when incinerated it releases dioxins and furans, two of the most carcinogenic compounds in existence. PVC by itself is so brittle that it is virtually useless but when combined with other chemicals it can convert into an almost limitless range of applications. It could be made into the stiff planks used to side houses, the strong pipes that carry water, the insulating coating of electrical wires, the squeezable arms of a doll, or the soft drapes of a shower curtain. Such versatility has made PVC one of the top-selling plastics in the world and a frequent choice for makers of medical devices.

The material that caught Carl Walter's eye was a particular variety of vinyl known as plasticized PVC, where the plastic is soft and pliable through the addition of a clear, oily liquid called di-(2-ethylhexyl) phthalate (DEHP), a member of the phthalate family. Phthalates have become so ubiquitous in consumer and industrial products that manufacturers make nearly half a billion pounds each year, and they are used as plasticizers, lubricants, and solvents. Phthalates are found in anything made of soft vinyl. They are used for food packaging and food processing equipment, as well as in construction materials, clothing, household furnishing, wallpaper, toys, personal care products (cosmetics, shampoos, perfume), adhesives, insecticides, waxes, inks, varnishes, lacquers, coatings, paints, and time-released coatings for medications and nutritional supplements. There are about 25 different types of phthalates, but only about six are widely used. Of them, DEHP is one of the most popular, especially

for medical uses. Carl Walter found that plasticized PVC was durable, flexible, and, unlike glass, did not damage red blood cells. It permitted the carbon dioxide in the blood to dissipate and oxygen to disperse, a fact also good for the blood cells. He considered the material completely inert. To persuade his colleagues, he brought a blood-filled bag to a meeting, dropped it on the floor, and then stepped on it. The bag held, which in itself was a huge advantage over breakable glass. The real advance, however, was that several bags could be connected to form a secure, sterile system through which blood could be separated for the first time into its various components: erythrocytes, plasma, and platelets. The new technology revolutionized the collection and use of blood. By the mid-1960s, PVC blood bags were standard in civilian blood banks and hospitals. Walter's intervention also began rippling through the field of intravenous therapy. Medical suppliers gradually switched out glass for PVC to hold a wide range of fluids delivered intravenously, from saline to drugs to nutritional supplements.

Phthalates are endocrine disruptors and the effects could be transgenerational. They depend on the timing of exposure and could become apparent only in offspring. At least 30 chemicals were identified as endocrine disruptors. Today, that number may be as high as 1000. By mimicking natural hormones, they can insinuate themselves into special receptors on cells that activate certain genes or they can block a natural hormone en route to its destination, preventing it from delivering its chemical message to the cellular receptor.

Aside from the phthalates, one of the most infamous suspects now is bisphenol A, the primary component of polycarbonate, a hard, clear plastic that is used to make a host of consumer items, including baby bottles, compact discs, eyeglass lenses, and water bottles. Bisphenol A is also a basic ingredient of the epoxy resins used to line canned foods and drinks. Bisphenol A acts a weak estrogen, such that it can disrupt how the body uses and produces natural estrogen. Water bottles made of polyethylene terephthalate (PET) seem to leach small amounts of one or more unknown compounds that mimic estrogen. Unfortunately, there is no way for consumers to know what chemicals are in the plastic items. Manufacturers generally are not required to list the ingredients of their plastic products.

Many suspected endocrine disruptors interfere with estrogen. DEHP, the chemical found in intravenous bags and tubing, is an antiandrogen, meaning that it interferes with testosterone and other masculinizing hormones. The medical devices may be a significant source of exposure, but most of us encounter DEHP through its nonmedical deployment in such vinyl items as shower curtains, wallpaper, venetian blinds, floor tiles, upholstery, garden hoses, swimming pool liners, rainwear, car upholstery and convertible tops, the sheathing on cables and wires, flip-flops, plastic shoes, modeling clay, yoga mats, cosmetics and nail polish, cleaning products, lubricants, and waxes. Our primary exposure may

be through fatty foods, such as cheese and oils that are particularly likely to absorb the chemical.

During these recent years, humans' exposure to DEHP and other phthalates has undoubtedly increased, given their steadily rising production and use. The result is that at least 80% of Americans of all ages and races, from city dwellers to rural dwellers, now carry measureable traces of DEHP and other phthalates in their bodies. Phthalates have been detected in blood, urine, saliva, breast milk, and amniotic fluid, which means that people are exposed to all chemicals in all stages of life, starting in utero. Our cells are under continual low-level assault. The group at greatest risk are newborns undergoing treatment in a NICU. A baby hooked up to an intravenous bag and tubing for weeks at a time may end up absorbing doses of DEHP 100 to 1000 times higher than those of the general population. The chemical hit is even larger if the newborn gets blood transfusions or later has to be connected to a heart/lung machine that circulates and oxygenates the blood in the body. The transfused blood is laced with DEHP from the blood bags. As the blood circulates through the heart/lung device, it flows through several dozen feet of plastic tubing and a plastic membrane, all of which leach DEHP. A sick baby getting that kind of intensive treatment can accumulate exposure 20 times higher than the level deemed safe for human intake. People of any age undergoing kidney dialysis and blood transfusions are at risk for getting a significant blast of DEHP.

The Centers for Disease Control and Prevention has pointed out that the mere presence of DEHP and any chemicals in anyone's blood or urine does not mean it is a health hazard. The big and difficult question is whether the small amounts that we are regularly exposed to are sufficient to affect someone's health. "We may all be a little plastic," as Freinkel indicates.

The above is a small portion of the pearls of this splendid book by Susan Freinkel.

SKIPPING BREAKFAST AND CARDIOVASCULAR DISEASE

Rong and colleagues³ from Wuhan, China, and Iowa City, Iowa, studied adults aged 40 to 75 years from 1988 to 1994 and asked them via an in-house interview how often they ate breakfast. Among the 6550 participants (mean age 53 years, 48% men), breakfast was never consumed in 5%, rarely consumed in 11%, consumed some days in 25%, and consumed every day in 59%. During follow-up, 2318 died, including 619 from cardiovascular disease. The participants who never consumed breakfast compared with those consuming breakfast every day had an 87% higher chance of dying from cardiovascular disease and a 19% higher chance of dying from any cause. Thus, in a follow-up of 17 to 23 years, skipping breakfast was associated with a significantly increased frequency of dying from cardiovascular disease. Eat breakfast.

INACTIVITY IN THE USA

Americans are becoming increasingly sedentary, spending almost a third of their waking hours sitting down, and computer use is partly to blame.⁴ The average daily sitting time for US teens is now 8 hours per day and for adults, almost 6.5 hours. The estimated prevalence of spending at least 2 hours per day watching television or videos in 2016 was 62% in children, 59% in adolescents, 62% in adults aged 20 to 64, and 84% in those aged ≥ 65 . The estimated prevalence of computer use outside school or work for at least 1 hour per day in 2016 was 56% for children, 57% for adolescents, and 50% for adults. It is not surprising that two-thirds of Americans are overweight.

EARLY RETIREMENT

Most people look forward to retirement, a reward for decades of hard work. Unfortunately, like many other pleasures, it may be bad for our health.⁵ Many retirees indulge in unhealthy behaviors, such as too much sitting, watching television, eating, drinking alcohol, and smoking. Without fulfilling work, retirees can feel adrift, become depressed, and risk becoming socially isolated. Without the intellectual stimulation that work can provide, retirement can accelerate cognitive decline. A study randomly forcing some workers to retire and others to remain in the labor force would provide the best evidence, but that kind of study is nearly impossible. Many studies, however, clearly show that health problems intensify after workers qualify for retirement benefits and abate after policies encouraging working longer are introduced.

One study examined how mortality rates changed at age 62, when one can first begin collecting Social Security retirement benefits. The investigators found that men are 2% more likely to die in the month they turn 62 than in the previous month. This mortality surge derives largely by an increase in deaths from lung cancer and chronic obstructive pulmonary disease, the major detrimental effect of cigarette smoking. A decrease in physical activity has its effect. In one study, 5-year mortality rates dropped for Americans aged 62 to 65 in those who continued to work vs. those who retired. At highest risk of dying within 5 years were nonworking men, followed by nonworking women, and the risk was lowest in employed women and next lowest in working men. The risk of antidepressants prescribed within 5 years was highest in women not working, followed by women working, men not working, and men working. When men in their early 60s delay retirement 5 years, the mortality risk decreases by 32%. Additionally, the average boost in future annual retirement income increases 9% when retirement is delayed another year.

The biggest downside of retirement is financial. Social Security replaces only about 40% of a paycheck received while working. Employer pensions are less common today than in the past, and relatively few people have saved enough to guarantee a financially secure old age. Workers who extend their careers can save part of their additional earning

for retirement and can accumulate more Social Security credit. Retirement savings do not have to last as long when workers delay retirement.

THE MOMENT OF LIFT

Growing up partly in Dallas, Texas, as the daughter of an Apollo program engineer, Melinda Gates (1964–) watched many space launches.⁶ She became fascinated by the “moment of lift” when the forces pushing a rocket up overtook the forces pushing it down. Today, she is co-chair of the Bill and Melinda Gates Foundation, which began in 2000 and gives billions of dollars annually to tackle extreme poverty. Some forces, like conflict and disease, keep people downtrodden. Others, like education and technology, encourage opportunity and economic growth. In the last 2 decades, she and her husband have visited poor communities around the world and have studied people’s daily lives. She writes in her 273-page book, “If you want to lift up humanity, empower women. It is the most comprehensive, pervasive, high-leverage investment you can make in human beings.” Ms. Gates spends much of the book addressing how gender-related disparities prevent equal opportunities and foster poverty. She discusses child marriage, domestic violence, and the anguish of poverty.

The Gates Foundation began its focus on gender-related disparities in agriculture. Ms. Gates learned that women do most of the farm work around the world and that their yields are 20% to 30% lower than those of men because they do not have the same access to tools and information as men. Women in traditional societies often lack the time to attend training sessions (because of their domestic responsibilities) and the social permission to talk to male experts sent by governments and charities. If women could grow crops as productively as men do, Ms. Gates observes, they would be better able to feed their families and send more children to school.

Access to contraception is a low-hanging fruit. Ms. Gates, an observant Catholic, treads carefully here. When she started talking with underdeveloped world mothers about vaccines, they would switch the topic to family planning and the frustration they felt when remote clinics ran out of contraceptive supplies. These mothers were “desperate not to get pregnant because they couldn’t take care of the kids they already had. ... When women in developing countries spaced their births by at least 3 years, each baby is almost twice as likely to survive their first year and 35% more likely to see their fifth birthday.”

While most of *The Moment of Lift* highlights the challenges of poor communities, Ms. Gates also shares her own journey to becoming an advocate for women and girls. She experienced firsthand the male-dominated world of Microsoft. Melinda French was one of the first female MBAs hired at Microsoft and was managing 1700 people when she left the company in 1996 to marry Bill Gates. Her account of thriving in a tech-macho culture is one of the most fascinating parts of the book. Her work environment was brash,

argumentative, and competitive. Rather than leave, she and other women went about changing what they could: being honest about their strengths and weaknesses.

The Moment of Lift is a very readable account of Ms. Gates' insights from the world's harshest corners and of the reasons why she is hopeful that progress is possible.

CRITERIA FOR EXCELLENCE

A few years ago, a friend of mine was head of the committee of one of the heart organizations charged with choosing a new editor in chief for one of its journals. When I saw him later, I asked, "What criteria did you use to pick the new editor?" He replied, "None." I have thought about his answer many times. Picking an editor, of course, is a crapshoot just like that of many other high positions.

Recently, I acquired the book *The Presidents: Noted Historians Rank America's Best—and Worst—Chief Executives* by Brian Lamb, Susan Swain, and C-SPAN.⁷ The book consists of 44 biographies of presidents initially interviewed on C-SPAN by nationally recognized historians or biographers. The chapters are organized according to the number of each president's 2017 rating determined by 91 presidential historians and professional observers of the presidency. They rated the presidents on 10 presidential leadership qualities established in 2000, also by a team of professional historians: Douglas Brinkley, Edna Greene Medford, Richard Norton Smith, and Robert X. Browning. Prior surveys in 2000 and 2009 used the same criteria for rating the presidents.

The 10 qualities of presidential leadership identified by these historians included the following: public persuasion, crisis leadership, economic management, moral authority, international relations, administrative skills, relations with Congress, vision/setting an agenda, pursuing equal justice for all, and performance within the context of the times. The top place went to Abraham Lincoln, and the worst to his predecessor, James Buchanan. All of these ratings are difficult, and some presidents rated better in some surveys than in others.

We need to develop clear criteria for being an excellent physician. This too would be difficult because medicine is such a broad arena. How would an ophthalmologist rate compared to an internist? The qualities that make a good internist may not be the qualities that make a superb surgeon. At any rate, it is a thought.

ATHLETIC SCHOLARSHIPS TO COLLEGES

Parents, do not count on it! Only 2% of high school athletes receive college scholarships in their sport, and that includes those awards well short of the "full ride" many parents covet.⁸ The ratios of high school athletes to college student athletes on scholarship in 2016–2017 by sport were the following: basketball, 64 high school athletes to 1 scholarship; soccer, 59:1; baseball, 36:1; football, 31:1; and hockey, 30:1. A 2019 survey on the cost of youth sports by TD Ameritrade indicated that 40% of parents said they felt

confident their child would get an athletic scholarship to college. The survey also found that parents were willing to cut back on spending, go into credit card debt, or delay retirement to fund their child's sport. The cost for families depends on the sport. While baseball parents spend on average \$4041 per child a year, volleyball parents can spend as much as \$8000 per child (2016 numbers). It is more worthwhile to simply study hard.

DOMESTIC MIGRATION TO TEXAS

The Texas state demographer and director of the Texas Demographic Center at the University of Texas at San Antonio has indicated that for nearly a decade, Texas has led all states in net domestic migration, resulting in an estimated 1,019,434 new residents moving into Texas between 2010 and 2017, or 385 per day, and the influx has not subsided.⁹ Between 2010 and 2014, the metro area of Dallas–Fort Worth–Arlington saw an increase of >23,000; Houston, >30,000; Austin, >20,000; and San Antonio, nearly 9,000. These numbers show that migration from outside the state is fueling urbanization in Texas. The state's metro regions garnered 94% of the total domestic migration between 2010 and 2014. Most new residents came from California, Florida, Louisiana, Illinois, and New York. More than 63,000 people moved from California to Texas in 2017 alone.

Why do so many domestic migrants come to Texas? Texas' major cities provide a high quality of life and a lower cost of living than those in California and New York. And, the influx of highly educated people has established influential hubs of industry in sectors as diverse as technology, telecommunications, health care, higher education, and energy. With tech companies such as AT&T, Dell, NEC, and Texas Instruments based in Texas, combined with a thriving startup scene in Austin, the state is becoming an increasingly important epicenter. Great ideas exist wherever great minds gather, and Texas is well positioned to be that watering hole.

William Clifford Roberts, MD
May 10, 2019

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