CHAPTER TWENTY-ONE

IN 1918 IN PARTICULAR, influenza struck so suddenly that many victims could remember the precise instant they knew they were sick, so suddenly that throughout the world reports were common of people who toppled off horses, collapsed on the sidewalk.

Death itself could come so fast. Charles-Edward Winslow, a prominent epidemiologist and professor at Yale, noted, "We have had a number of cases where people were perfectly healthy and died within twelve hours." The *Journal of the American Medical Association* carried reports of death within hours: "One robust person showed the first symptom at 4:00 P.M. and died by 10:00 A.M." In *The Plague of the Spanish Lady: The Influenza Pandemic of 1918-1919,* writer Richard Collier recounted this: In Rio de Janeiro, a man asked medical student Ciro Viera Da Cunha, who was waiting for a streetcar, for information in a perfectly normal voice, then fell down, dead; in Cape Town, South Africa, Charles Lewis boarded a streetcar for a three-mile trip home when the conductor collapsed, dead. In the next three miles six people aboard the streetcar died, including the driver.

Lewis stepped off the streetcar and walked home.

It was the lungs that had attracted attention from pathologists first. Physicians and pathologists had many times seen lungs of those dead of pneumonia. Many of the deaths from influenzal pneumonia did look like

these normal pneumonias. And the later in the epidemic a victim died, the higher was the percentage of autopsy findings that resembled normal pneumonia, bacterial pneumonia.

Those who died very quickly, a day or even less after the first symptoms, however, most likely died of an overwhelming and massive invasion of the virus itself. The virus destroyed enough cells in the lung to block the exchange of oxygen. This alone was unusual and puzzling. But the lungs of the men and women who died two days, three days, four days after the first symptom of influenza bore no resemblance to normal pneumonias at all. They were more unusual, more puzzling.

In April a Chicago pathologist had sent lung-tissue samples to the head of a research institute and asked him "to look over it as a new disease." British pathologists in France had commented on strange autopsy findings in the spring. Capps had mentioned unusual findings in the lungs to Welch, Cole, and other members of the inspection party in June. The lungs Welch himself had seen in the Devens autopsy room had made him fear that the disease was a new one.

The respiratory tract serves a single purpose: to transfer oxygen from the air into red blood cells. One can picture the entire system as an inverted oak tree. The trachea—the windpipe—carries air from the outside world into the lungs and is the equivalent of the tree trunk. This trunk then divides into two great branches, each called a "primary bronchus," which carry oxygen into the right and left lungs. Each primary bronchus subdivides into smaller and smaller bronchi, smaller branches, as they enter the lungs until they become "bronchioles." (Bronchi have cartilage, which helps give the lung a kind of architectural structure; bronchioles do not have cartilage.)

Each lung itself subdivides into lobes—the right lung has three, the left only two. The lobes subdivide into a total of nineteen smaller pockets. Within these pockets, sprouting like leaves from the smaller bronchi and the bronchioles, are clusters of tiny sacs called alveoli. They are much like tiny but porous balloons, and the average person has 300 million of them. The alveoli play a role comparable to that which leaves play in photosynthesis. In the alveoli, the actual transfer of oxygen into the blood takes place.

The right side of the heart pumps blood without oxygen into the lungs, where it passes into capillaries, the smallest blood vessels, so small that

individual blood cells often move in single file. Capillaries surround the alveoli, and oxygen molecules slip through the membrane of the alveolar tissue and attach to the hemoglobin of the red blood cells as they circulate past them. After picking up oxygen, the blood returns to the left side of the heart, where it is pumped through arteries throughout the body. (The body's entire blood supply moves through the lungs each minute.)

In arteries, red blood cells carry oxygen and are bright red; in veins, such as those visible on one's wrist, the same cells without oxygen are bluish. When the lungs fail to oxygenate the blood, part of the body, and in some cases the entire body, can turn blue, causing cyanosis. Lack of oxygen, if extended for any length of time, damages and ultimately kills other organs in the body.

Healthy lung tissue is light, spongy, and porous, much lighter than water, and a good insulator of sound. A physician percussing the chest of a healthy patient will hear little. When normal lung tissue is manipulated, it "crepitates": as the air in the alevoli escapes, it makes a crackling noise similar to rubbing hairs together.

A congested lung sounds different from a healthy one: solid tissue conducts breathing sounds to the chest wall, so someone listening can hear "rales," crackling or wheezing sounds (although it can also sound either dull or hyperresonant). If the congestion is dense enough and widespread enough the lung is "consolidated."

In bronchopneumonia, bacteria—and many kinds of bacteria can do this—invade the alveoli themselves. Immune-system cells follow them there, and so do antibodies, fluid, and other proteins and enzymes. An infected alveolus becomes dense with this material, which prevents it from transferring oxygen to the blood. This "consolidation" appears in patches surrounding the bronchi, and the infection is usually fairly localized.

In lobar pneumonia, entire lobes become consolidated and transformed into a liverlike mass—hence the word "hepatization" to describe it. A hepatized lobe can turn various colors depending on the stage of disease; grey hepatization, for example, indicates that various kinds of white blood cells have poured into the lung to fight an infection. A diseased lung also includes the detritus of dissolved cells, along with various proteins such as fibrin and collagen that are part of the body's efforts to repair damage. (These repair efforts can cause their own problems. "Fibrosis" occurs when too much fibrin interferes with the normal functioning of the lung.)

Roughly two-thirds of all bacterial pneumonias and an even higher percentage of lobar pneumonias are caused by a single group of bacteria, the various subtypes of the pneumococcus. (The pneumococcus is also the second leading cause of meningitis.) A virulent pneumococcus can spread through an entire lobe within a matter of hours. Even today, in 20 to 30 percent of the cases of lobar pneumonia, bacteria also spread through the blood to infect other areas of the body, and many victims still die. Some cyanosis is not unusual in lobar pneumonia, but most of the lung often still looks normal.

In 1918 pathologists did see at autopsy the normal devastation of the lungs caused by the usual lobar and bronchopneumonias. But the lungs from those who died quickly during the pandemic, the lungs that so confused even Welch, those lungs were different. Said one pathologist, "Physical signs were confusing. Typical consolidation was seldom found." And another: "The old classification by distribution of the lesions was inappropriate." And another: "Essentially toxic damage to alevolar walls and exudation of blood and fluid. Very little evidence of bacterial action could be found in some of these cases."

At a discussion reported in the *Journal of the American Medical Association,* several pathologists concurred, "The pathological picture was striking, and was unlike any type of pneumonia ordinarily seen in this country. . . . The lung lesions, complex and variable, struck one as being quite different in character to anything one had met with at all commonly in the thousands of autopsies one had performed during the last 20 years."

Normally when the lungs are removed they collapse like deflated balloons. Not now. Now they were full, but not of air. In bacterial pneumonias, normally the infection rages inside the alveoli, inside the tiny sacs. In 1918, while the alveoli were also sometimes invaded, the spaces between the alveoli were filled. This space, which makes up the bulk of the volume of the lung, was filled with the debris of destroyed cells and with every element of the immune system, from enzymes to white blood cells. And it was filled with blood.

One more observer concluded that "the acute death" he saw evidence of in the lungs "is a lesion which does not occur in other types of pulmonary infection. In influenza it is the lesion of characterization."

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Victims' lungs were being ripped apart as a result of, in effect, collateral damage from the attack of the immune system on the virus. Since the respiratory tract must allow outside air to pass into the innermost recesses of the body, it is extremely well defended. The lungs became the battleground between the invaders and the immune system. Nothing was left standing on that battleground.

The immune system begins its defense far in advance of the lungs, with enzymes in saliva that destroy some pathogens (including HIV, which makes its home in most bodily fluids, but not in saliva, where enzymes kill it). Then it raises physical obstacles, such as nasal hairs that filter out large particles and sharp turns in the throat that force inhaled air to collide with the sides of breathing passageways.

Mucus lines these passageways and traps organisms and irritants. Underneath the layer of mucus lies a blanket of "epithelial cells," and from their surfaces extend "cilia," akin to tiny hairs which, like tiny oars, sweep upward continuously at from 1,000 to 1,500 beats a minute. This sweeping motion moves foreign organisms away from places they can lodge and launch an infection, and up to the larynx. If something does gain a foothold in the upper respiratory tract, the body first tries to flush it out with more fluid—hence the typical runny nose—and then expel it with coughs and sneezes.

These defenses are as physical as raising an arm to block a punch and do no damage to the lungs. Even if the body overreacts, this usually does no serious harm, although an increased volume of mucus blocks air passages and makes breathing more difficult. (In allergies these same symptoms occur because the immune system does overreact.)

There are more aggressive defenses. Macrophages and "natural killer" cells—two kinds of white blood cells that seek and destroy all foreign invaders, unlike other elements of the immune system that only attack a specific threat—patrol the entire respiratory tract and lungs. Cells in the respiratory tract secrete enzymes that attack bacteria and some viruses (including influenza) or block them from attaching to tissue beneath the mucus, and these secretions also bring more white cells and antibacterial enzymes into a counterattack; if a virus is the invader, white blood cells also secrete interferon, which can block viral infection.

All these defenses work so well that the lungs themselves, although directly exposed to outside air, are normally sterile.

But when the lungs do become infected, other defenses, lethal and violent defenses, come into play. For the immune system is at its core a killing machine. It targets infecting organisms, attacks with a complex arsenal of weapons—some of them savage weapons—and neutralizes or kills the invader.

The balance, however, between kill and overkill, response and overresponse, is a delicate one. The immune system can behave like a SWAT team that kills the hostage along with the hostage taker, or the army that destroys the village to save it.

In 1918 especially, this question of balance played a crucial role in the war between virus and immune system, and between life and death. The virus was often so efficient at invading the lungs that the immune system had to mount a massive response to it. What was killing young adults a few days after the first symptom was not the virus. The killer was the massive immune response itself.

The virus attaches itself normally to epithelial cells, which line the entire respiratory tract like insulation in a tube all the way to the alveoli. Within fifteen minutes after influenza viruses invade the body, their hemagglutinin spikes begin binding with the sialic-acid receptors on these cells. One after another these spikes attach to the receptors, each one a grappling hook binding the virus tighter and tighter to the cell. Generally about ten hours after the virus invades a cell, the cell bursts open, releasing between 1,000 and 10,000 viruses capable of infecting other cells. At even the lowest reproduction rate—1,000 times 1,000 times 1,000, and so on—one can easily understand how a victim could feel perfectly healthy one moment and collapse the next, just as the fifth or sixth generation of viruses matures and infects cells.

Meanwhile, the virus is also attacking the immune system directly, undermining the body's ability to protect itself; the virus inhibits the release of interferon, and interferon is usually the first weapon the body employs to fight viral infection. In 1918 the ability to inhibit the immune system was so obvious that researchers, even while overwhelmed by the pandemic, noticed that influenza victims had weakened immune responses to other stimuli; they used objective tests to prove it.

Even mild influenza viruses can utterly and entirely denude the upper respiratory tract of epithelial cells, leaving it bare, stripping the throat raw. (The repair process begins within a few days but takes weeks.)

Once an infection gains a foothold, the immune system responds initially with inflammation. The immune system can inflame at the site of an infection, causing the redness, heat, and swelling there, or it can inflame the entire body through fever, or both.

The actual process of inflammation involves the release by certain white blood cells of proteins called "cytokines." There are many kinds of white cells; several kinds attack invading organisms, while other "helper" cells manage attacks, and still others produce antibodies. There are even more kinds of cytokines. Some cytokines attack invaders directly, such as interferon, which attacks viruses. Some act as messengers carrying orders. Macrophages, for example, release "GM CSF," which stands for "granulocyte-macrophage colony-stimulating factor"; GM CSF stimulates the production in the bone marrow of more macrophages as well as granulocytes, another kind of white blood cell. Some cytokines also carry messages to parts of the body not normally considered belonging to the immune system; several cytokines can affect the hypothalamus, which acts like the body's thermostat. When these cytokines bind to receptors in the hypothalamus, body temperature goes up; the entire body becomes inflamed. (Fever is part of the immune response; some pathogens do not grow well at higher temperatures.) In influenza, fever routinely climbs to 103, and can go higher.

But cytokines themselves also have toxic effects. The typical symptoms of influenza outside the respiratory tract, the headache and body ache, are caused not by the virus but by cytokines. A side effect of cytokines' stimulating the bone marrow to make more white cells, for instance, is likely what aches in the bone.

Cytokines can cause more serious and permanent damage as well. "Tumor necrosis factor," to give one example, is a cytokine that gets its name from its ability to kill cancer cells—tumors exposed to TNF in the laboratory simply melt away; it also helps raise body temperature and stimulates antibody production. But TNF is extraordinarily lethal, and not just to diseased cells. It can destroy healthy ones as well. In fact, it can kill the entire body. TNF is a toxin and a major cause of toxic shock syndrome, and it is not the only toxic cytokine.

Routinely, the body fights off the influenza virus before it gains a solid foothold in the lungs themselves. But in 1918 the virus often succeeded in infecting epithelial cells not only in the upper respiratory tract but all the way down the respiratory tract into the innermost sanctuaries of the lungs, into the epithelial cells of the alveoli. This was viral pneumonia.

The immune system followed the virus into the lungs and there waged war. In this war the immune system held nothing back. It used all its weapons. And it killed. It killed particularly with "killer T cells," a white blood cell that targets the body's own cells when they are infected with a virus, and it killed with what is sometimes referred to as a "cytokine storm," a massive attack using every lethal weapon the body possesses.

The same capillaries that moved blood past the alveoli delivered this attack. The capillaries dilated, pouring out fluid, every kind of white blood cell, antibodies, other elements of the immune system, and cytokines into the lung. Then these cytokines and other enzymes virtually obliterated the capillaries. Even more fluid poured into the lung. The cells that line the alveoli were damaged, if they survived the virus itself. Pink glassy membranes, called hyaline membranes, formed on the insides of the alveoli. Once these membranes formed, "surfactant"—a slippery, soaplike protein that reduces surface tension and eases the transfer of oxygen into red blood cells—disappeared from the alveoli. More blood flooded the lungs. The body started producing fiberlike connective tissue. Areas of the lung became enmeshed in cell debris, fibrin, collagen, and other materials. Proteins and fluid filled the space between cells.

Macfarlane Burnet, the Nobel laureate, described what was happening inside the lungs: "acute inflammatory injection . . . very rapid necrosis of most of the epithelial lining of the bronchial tree down to and especially involving the smallest bronchioles. . . . Essentially toxic damage to alveolar walls and exudation of blood and fluid . . . [C]ontinued exudation of fluid in areas where blocking of smaller bronchi had occurred would produce eventually airless regions."

The immune system changes with age. Young adults have the strongest immune system in the population, most capable of mounting a massive immune response. Normally that makes them the healthiest element of the population. Under certain conditions, however, that very strength becomes a weakness.

In 1918 the immune systems of young adults mounted massive

responses to the virus. That immune response filled the lungs with fluid and debris, making it impossible for the exchange of oxygen to take place. The immune response killed.

The influenza outbreak in 1997 in Hong Kong, when a new virus jumped from chickens to humans, killed only six people and it did not adapt to man. More than a million chickens were slaughtered to prevent that from happening, and the outbreak has been much studied. In autopsies pathologists noticed extremely high cytokine levels, discovered even that the bone marrow, lymphoid tissue, spleen—all involved in the immune response—and other organs were themselves under attack from an immune system turned renegade. They believed that this proved "syndrome [was] not previously described with influenza." In fact, investigators in 1918 had seen the same thing.

This was still influenza, only influenza.

In the 1970s physicians began to recognize a pathological process in the lungs that could have many causes but, once the process began, looked the same and received the same treatment. They called it ARDS, which stands for Acute Respiratory Distress Syndrome. Almost anything that puts extreme stress on the lung can cause ARDS: near drowning, smoke inhalation, inhaling toxic fumes (or poison gas) . . . or influenzal viral pneumonia. Doctors today looking at pathology reports of lungs in 1918 would immediately designate the condition as ARDS.

One pulmonary expert describes ARDS as "a burn inside the lungs." It is a virtual scorching of lung tissue. When viral pneumonia causes the condition, the immune system toxins designed to destroy invaders are what, in effect, flame in the lung, scorching the tissue.

Whatever the causes of ARDS, even today there is no way of stopping the process of disintegration in the lung once it begins. The only care is supportive, keeping the victim alive until he or she can recover. This requires all the technology of modern intensive care units. Still, even with the best modern care, even with for example dramatically more efficient and effective administration of oxygen than in 1918, the mortality rate for ARDS patients in different studies ranges from 40 to 60 percent. Without intensive care—and hospitals have few beds in intensive-care units—the mortality rate would approach 100 percent.

(In 2003 a new coronavirus that causes SARS, "Severe Acute Respiratory Syndrome," appeared in China and quickly spread around the world. Coronaviruses cause an estimated 15 to 30 percent of all colds and, like the influenza virus, infect epithelial cells. When the coronavirus that causes SARS does kill, it often kills through ARDS, although since the virus replicates much more slowly than influenza, death from ARDS can come several weeks after the first symptoms.)

In ARDS, death can come from many causes. Organs outside the lungs fail because they get too little oxygen. The lungs can so fill with fluid that the right ventricle of the heart cannot empty it so the victim drowns. The strain of trying to pump blood out of the lung can cause heart failure. Or the victim can simply die from exhaustion: he or she must breathe so rapidly to get enough oxygen that muscles become exhausted. Breathing just stops.

ARDS by no means accounts for all the influenza deaths in 1918 and 1919, or even for a majority of them. It explains only those who died in a few days, and it explains why so many young healthy people died. Although influenza almost certainly killed some people in ways that had little to do with the lungs—for example, someone whose already weak heart could not stand the additional strain of fighting the disease—the overwhelming majority of non-ARDS deaths came from bacterial pneumonias.

The destruction of the epithelial cells eliminated the sweeping action that clears so much of the respiratory tract of bacteria, and the virus damaged or exhausted other parts of the immune system as well. That gave the normal bacterial flora of the mouth unimpeded entry into the lungs. Recent research also suggests that the neuraminidase on the influenza virus makes it easier for some bacteria to attach to lung tissue, creating a lethal synergy between the virus and these bacteria. And in the lungs, the bacteria began to grow.

Bacterial pneumonias developed a week, two weeks, three weeks after someone came down with influenza, including even a seemingly mild case of influenza. Often influenza victims seemed to recover, even returned to work, then suddenly collapsed again with bacterial pneumonia.

It is impossible to know what percentage of the dead were killed by a viral pneumonia and ARDS and how many died from bacterial pneumonias. Generally speaking, epidemiologists and historians who have writ-

ten about this pandemic have assumed that the overwhelming majority of deaths came from secondary invaders, from bacterial pneumonias that can be fought with antibiotics.

The conclusion of the army's pneumonia commission, however, is chilling in terms of implications for today. This commission, comprised of half a dozen of the finest scientists in America, both conducted autopsies and reviewed pathology reports of others; it found signs of what would today be called ARDS in almost half the autopsies. A separate study limited to the pathology of the disease, conducted by Milton Winternitz, a Welch protégé and later dean of the Yale Medical School, reached the same conclusion.

That overstates the proportion of victims who died from ARDS—in effect from influenzal viral pneumonia—because the army study looked only at deaths among soldiers, men who were young and otherwise healthy, the group most likely to have been killed by their own immune systems. In the total population, viral pneumonias and ARDS would not account for as high a percentage of the deaths. Most deaths almost certainly did come from secondary bacterial infections, but probably not quite so many as has been assumed. That should, however, be small comfort for those who worry about the next influenza pandemic.

The 1957 pandemic struck in the golden age of antibiotics, but even then just 25 percent of the fatalities had viral pneumonia only; three-quarters of the deaths came from complications, generally bacterial pneumonia. Since then bacterial resistance has become a major problem in medicine. Today the mortality rate for a bacterial pneumonia following influenza is still roughly 7 percent, and in some parts of the United States, 35 percent of pneumococcal infections are resistant to the antibiotic of choice. When staphylococcus aureus, a bacterium that has become particularly troubling in hospitals because of its resistance to antibiotics, is the secondary invader, the death rate—today—rises to as high as 42 percent. That is higher than the general death rate from bacterial pneumonias in 1918.

■ Part VII
THE RA

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