

People and Pigs

Iowa's Role in 20th-Century Influenza History

by Russell W. Currier

In the mid-18th century, Italians who contracted the dreaded disease, usually in early winter, called it *influenza di freddo*—"influenced by the cold." With medical advances in the 20th century, our understanding of viral influenza has improved greatly. Many of these insights and advancements evolved from Iowa connections.

The defining event of influenza in all time occurred in the fall of 1918 with the appearance of a new strain of flu. Upwards of half the human population of the world were affected and mortality rates of 2 to 5 percent were common among the affected. The disease was so severe that some patients progressed from onset to death in less than two days' time. A *Des Moines Evening Tribune* headline for October 8 solemnly announced 36 deaths at Camp Dodge and 5,624 cases.

A week earlier, on September 30, the National Swine Show and Exposition in Cedar Rapids opened to large crowds. Within a few days some of the swine exhibited an illness that was being transmitted to other pigs. The swine show was closed early due to the infectiousness. J. S. Koen, a livestock inspector in the U.S. Bureau of Animal Industry from Fort Dodge, realized that the illness had never been seen before, and he observed that it was similar to human influenza, which was sweeping the globe. Koen proposed that they were the same illness and named this new disease "swine influenza."

Hog producers were sensitive to the term "swine influenza," since it might convey that pork was unhealthy. Nevertheless, Koen was adamant. "I have no apologies to offer for my diagnosis of 'flu,'" he wrote a year later. "Last winter and fall we were confronted with a new condition, if not a new disease. . . . The similarity of the epidemic among people and the epizootic [an



ORIGINAL AT IOWA STATE UNIVERSITY ARCHIVES

Patients fill the makeshift hospital set up in the Iowa State College gymnasium in Ames during the 1918 influenza pandemic. The pandemic resulted in 20 million deaths worldwide, including 500,000 in the United States in less than a year. For young people, the 1918 flu strain was particularly virulent.

People and Pigs

Iowa's Role in 20th-Century Influenza History

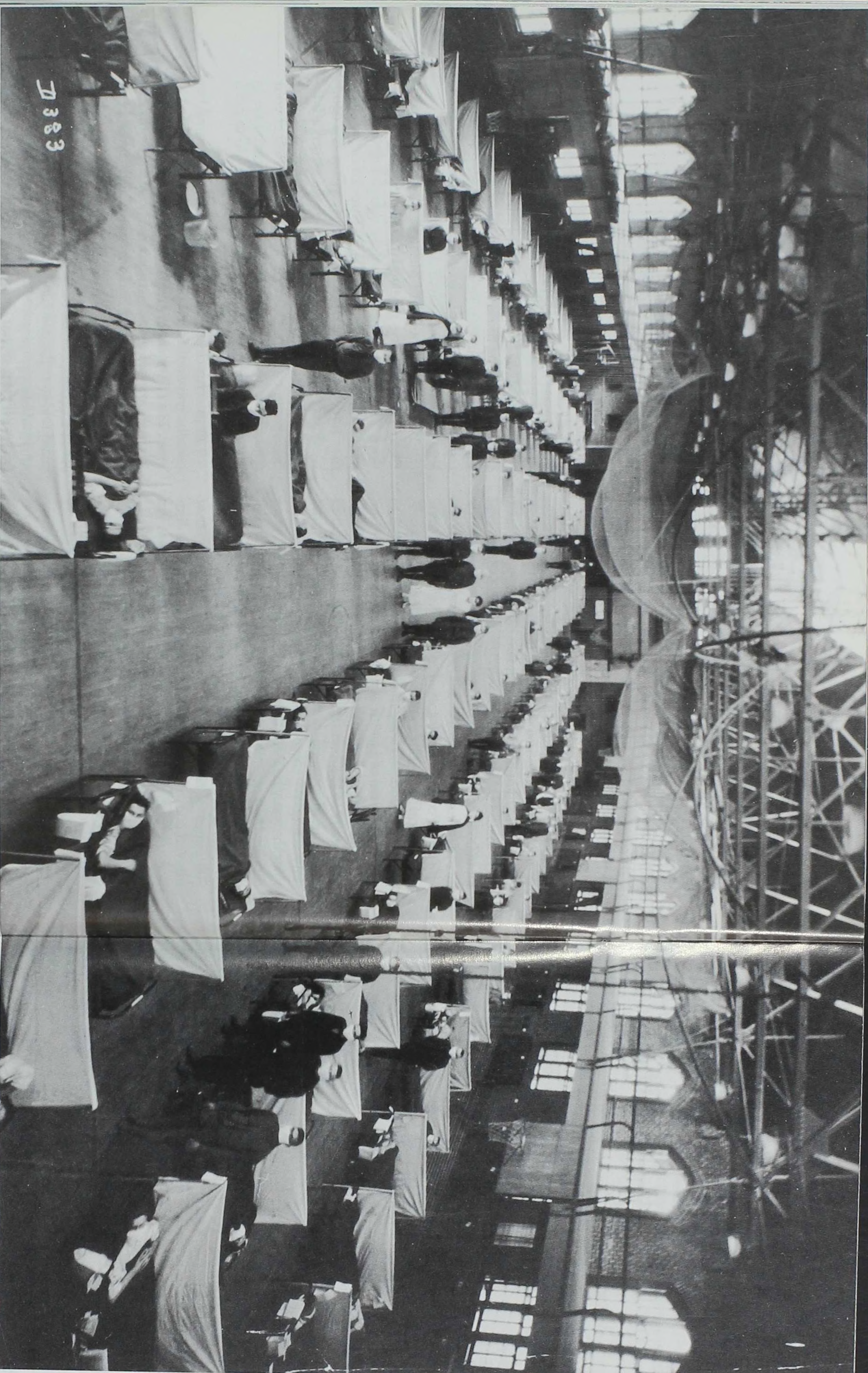
by Russell W. Currier

In the mid-18th century, Italians who contracted the dreaded disease, usually in early winter, called it *influenza di freddo*—"influenced by the cold." With medical advances in the 20th century, our understanding of viral influenza has improved greatly. Many of these insights and advancements evolved from Iowa connections.

The defining event of influenza in all time occurred in the fall of 1918 with the appearance of a new strain of flu. Upwards of half the human population of the world were affected and mortality rates of 2 to 5 percent were common among the affected. The disease was so severe that some patients progressed from onset to death in less than two days' time. A *Des Moines Evening Tribune* headline for October 8 solemnly announced 36 deaths at Camp Dodge and 5,624 cases.

A week earlier, on September 30, the National Swine Show and Exposition in Cedar Rapids opened to large crowds. Within a few days some of the swine exhibited an illness that was being transmitted to other pigs. The swine show was closed early due to the infectiousness. J. S. Koen, a livestock inspector in the U.S. Bureau of Animal Industry from Fort Dodge, realized that the illness had never been seen before, and he observed that it was similar to human influenza, which was sweeping the globe. Koen proposed that they were the same illness and named this new disease "swine influenza."

Hog producers were sensitive to the term "swine influenza," since it might convey that pork was unhealthy. Nevertheless, Koen was adamant. "I have no apologies to offer for my diagnosis of 'flu,'" he wrote a year later. "Last winter and fall we were confronted with a new condition, if not a new disease. . . . The similarity of the epidemic among people and the epizootic [an



ORIGINAL AT IOWA STATE UNIVERSITY ARCHIVES

Patients fill the makeshift hospital set up in the Iowa State College gymnasium in Ames during the 1918 influenza pandemic. The pandemic resulted in 20 million deaths worldwide, including 500,000 in the United States in less than a year. For young people, the 1918 flu strain was particularly virulent.

"During World War I, 1918 was a bad year of the flu. [At the University of Iowa Hospital in Iowa City] we lost five striped nurses and three white nurses, eight nurses altogether. . . . They brought students over and it seemed like the poor boys just died like flies. The hospital that was built for contagious diseases hadn't been opened, it was brand new. When the flu broke out they brought the students over and put them on the top floor thinking that would be safer up there from everybody else. It wasn't very long until the whole building was full. They'd bring them in the afternoon and maybe they'd be gone by morning. It just seemed to take them in no time."

—Bess Burrows

"It was terrible out there [at Camp Dodge in Des Moines]. That was one of the reasons why we were held up and they didn't send us overseas was because the flu was so terrible they were dying out there two or three hundred a day. They were hauling them in dray wagons down to the embalming station. They didn't have anything to put them in. They just wrapped them up in Army blankets and stacked them in the wagons, hauled them down to the mortuary where they put the bodies in rough boxes. They stacked the rough boxes outdoors. Oh, there was a row three wide, and about fifteen or sixteen long, and about eight or ten high."

—Claude Davis

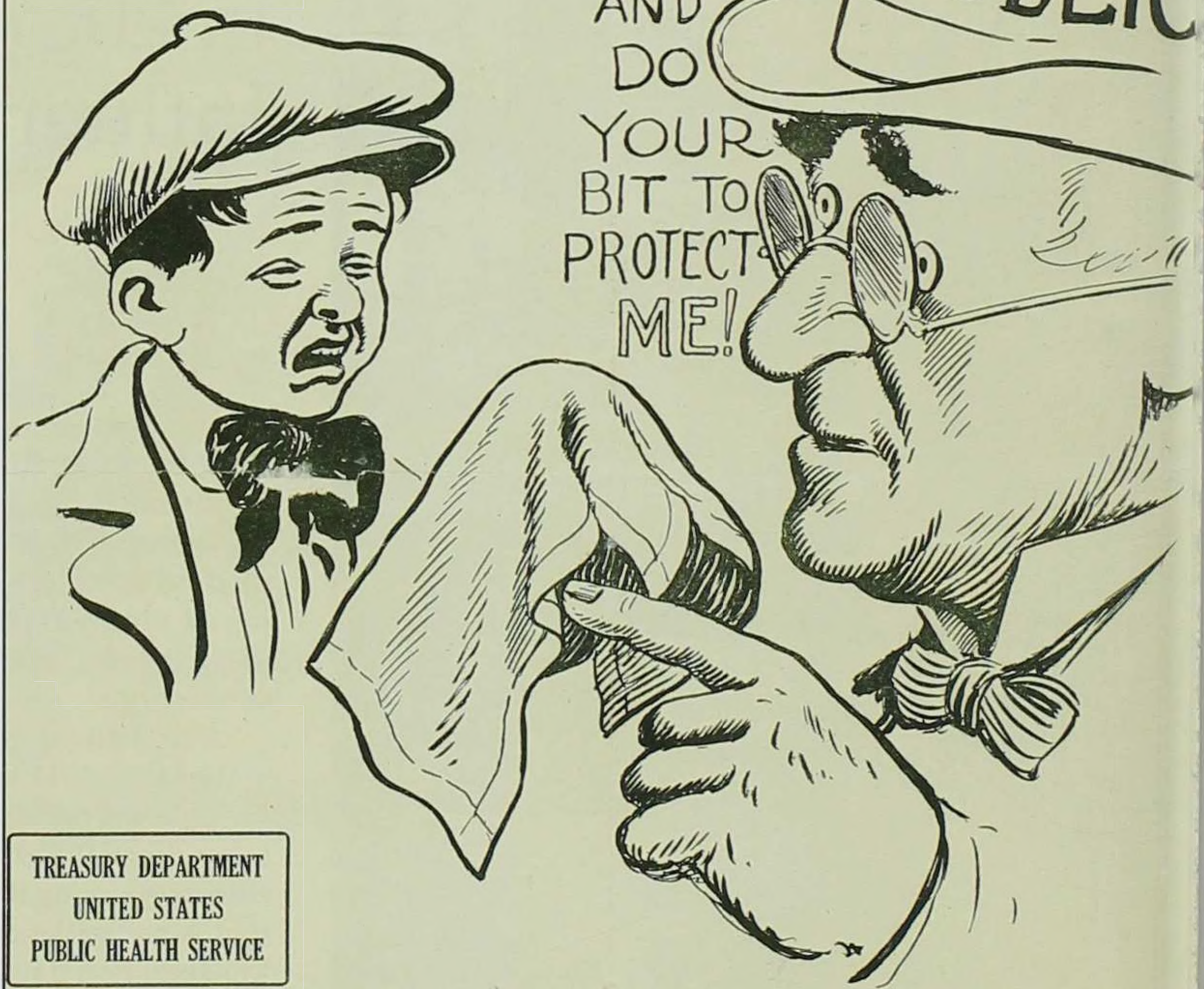
animal epidemic] among pigs was so close, the reports so frequent, that an outbreak among the hogs and vice versa, as to present a most striking coincidence, if not suggesting a close relation between the two conditions. It looked like 'flu,' it presented the identical symptoms of 'flu,' and until proved it was not 'flu,' I shall stand by that diagnosis." This new disease appeared in pigs annually after 1918.

Nine years later in 1927, an Iowa veterinarian with the U.S. Bureau of Animal Industry in Ames, C. N. McBryde, did field studies of swine influenza, noting the first symptoms as loss of appetite, "do not like to move," fever, a "thump or jerky respiration," and invariably a cough. Initially skeptical of Koen's linking of swine and human flu, McBryde later concurred when he suffered an influenza-like illness after extensive exposure to similarly affected swine. His illness was characterized by loss of appetite, slight fever, "aching in the back and joints," and a cough resembling whooping cough. "The cough was not troublesome at night, nor when resting quietly," he observed, "but the paroxysms seemed to be brought on by exertion and, in this respect, was quite similar in nature to the cough which is one of the characteristic symptoms of hog flu. This indisposition was so entirely different from the usual run of colds and was so similar in its sudden onset and in some of its symptoms to swine flu, that the writer has rather inclined to think it must have been a respiratory infection acquired as a result of breathing the dusty atmosphere of the hog barns occupied by swine suffering from acute hog flu."

Another Iowan, a young physician, read Koen's papers and was intrigued. A graduate from the State University of Iowa College of Medicine, Richard Shope

**USE
THE HANDKERCHIEF
AND DO
YOUR
BIT TO
PROTECT
ME!**

**THE
PUBLIC**



TREASURY DEPARTMENT
UNITED STATES
PUBLIC HEALTH SERVICE

**COLDS, INFLUENZA, PNEUMONIA, AND
TUBERCULOSIS ARE SPREAD THIS WAY**

Poster Series No. 2.

GOVERNMENT PRINTING OFFICE

Public health departments reminded Americans that such simple measures as using a handkerchief helped prevent the spread of influenza and other diseases. Researching the various strains and producing vaccines is far more complex.

taught pharmacology at the university before being recruited by the Rockefeller Institute at Princeton, where he worked on treatment of human tuberculosis. Shope was dispatched back to Iowa in the fall of 1928 to do field studies on hog cholera, a serious disease of pigs at this time. On this trip he observed swine influenza in Iowa.

"In the summer of 1928," Shope recounted, "I was in Iowa doing blood counts in hog cholera and other

swine disease with the cooperation of a number of veterinarians in eastern Iowa. During this time I had occasion to go to Ames to see Dr. Charles Murray and it was he who first called my attention to the existence of swine influenza. Returning to eastern Iowa, arrangements were made with Dr. Fred Crow for the collection of material from typical cases when the epizootic should appear during the autumn. Dr. Crow telegraphed me on November 13 saying, 'Plenty of hog flu—come at once.' I took the first train west, and on arriving in Iowa City found that there was indeed plenty of 'hog flu.' Through the friendliness and cooperation of a number of eastern Iowa veterinarians and their clients, many swine autopsies were obtained and material from the best cases was shipped back to Princeton. At that time, because we had no idea as to how fragile or easily killed the causative agent might be, we packed our infectious material in iced thermos jugs and sent it by air mail from Cedar Rapids. After several unsuccessful attempts to establish swine influenza in our experimental pigs in Princeton with the various samples sent, one batch finally 'took.' This had been obtained by Dr. Crow on the Probst Brothers' farm near Iowa City. Dr. Lewis, my chief, wired me of his success in establishing the disease experimentally and to return to Princeton as soon as possible."

Shope also recovered a bacterium from pigs with flu that closely resembled a comparable microorganism (Pfeiffer's bacillus) isolated from patients with influenza. This bacterium had been associated with a number of human influenza cases in the fall of 1918; many considered it the cause of influenza.

Later in 1931, Shope conclusively demonstrated the presence of a new virus that was important in causing swine influenza. He later recommended that British scientist Christopher Andrewes (who was working on human influenza) should test ferrets, which can be highly susceptible to human influenza virus. Andrewes and his colleagues subsequently established that a virus caused human influenza. Shope's research on swine influenza set the protocols for subsequent human flu studies.

Shope also looked back to the 1918 flu epidemic. The earlier and smaller wave of the flu in the spring of 1918 was less severe and seemingly conferred immunity to the more lethal strain in the fall. Shope noted in a 1958 lecture that "the 2nd Infantry Regiment . . . underwent influenza in June of 1918 in Hawaii before being transferred to Camp Dodge [in Des Moines] about August 1. When the severe second wave hit Camp Dodge in September and October, the 2nd Regiment was only slightly affected, although the attack rate for the

camp as a whole was about 33 percent and the case fatality [rate] 6.8 percent."

In 1949 Swedish graduate student Johan Hultin and his wife, Gunvor, were on their way to the State University of Iowa, where Hultin would conduct research on the influenza virus. After hearing an off-hand remark by scientist William Hale suggesting that the 1918 flu virus might be recovered from flu victims buried in permafrost (freezing preserves virus), Hultin proposed an expedition to Alaska to locate native villages decimated by the 1918 influenza pandemic and to exhume victims who were buried in permafrost.

The goal was to recover the original strain of the 1918 virus for study and possible use as seed virus for vaccine production. In June 1951, Hultin, with University of Iowa virologist Albert McKee and pathologist Jack Layton, departed for Fairbanks. They would meet up with Otto Geist, a German paleontologist who was familiar with areas affected by the flu.

There was a sense of urgency and competition. The U.S. Army, with elaborate funding and technical support from the National Institutes of Health, was organizing a major expedition to accomplish a similar scenario, using Hultin's information submitted as part of a funding request.

Several days of continuous rain delayed Hultin's flight to the villages of Wales and Brevig. Eventually the rain stopped and a bush pilot flew him in to Wales, where 178 of 396 residents had died from the 1918 influenza within a few weeks. The grave site was no longer in permafrost owing to beach erosion. Next Hultin flew to Brevig, where 72 of 80 people died of flu in November 1918. The bodies had been stored above ground for two months until Alaska territorial authorities contracted with a gold-mining company to excavate a burial site six feet below the surface.

Hultin met with village leaders and missionaries to explain the need and potential good of exhumation and collection of tissues. After permission was granted, Hultin worked 16 to 18 hours a day to slowly remove the frozen soil. He then sent for McKee and Layton to help collect tissue.

Because the team's dry ice for preserving specimens had evaporated early on the trip, Hultin appropriated fire extinguishers. The white cloud sprayed from fire extinguishers was in fact powdered dry ice; they quickly filled thermos containers with it.

After restoring the grave site, Hultin, McKee, and Layton flew back to Iowa, making numerous stops to recharge their specimen containers with more dry ice

from fire extinguishers. Back in Iowa City, Hultin started the exciting work of trying to grow virus in the embryos of fertile chicken eggs. Nothing grew. Next he injected tissue suspensions into the nostrils of guinea pigs, ferrets, and white mice. After several attempts, no viable virus was recovered and all the tissue specimens were exhausted. The larger, well-funded U.S. Army expedition to exhume corpses had also failed.

Hultin set his work aside, completed his medical education at Iowa, and moved to California. He thought he was through with his Alaska expeditions.

After about 1920, influenza activity had returned to its pre-1918 character: it consistently appeared in the late fall and early winter and had a low mortality rate. Then, in the spring of 1957, a major shift was detected. The Walter Reed Army Institute identified influenza viruses from Hong Kong cases that were distinctly different from earlier strains. In June sporadic cases were identified on both the East and West Coast of the United States. The race was on to produce an "Asian flu" vaccine in time for peak flu season, December through February. Unfortunately, "seeding" (the initial spread of the virus) had already occurred, in Grinnell, Iowa.

Beginning on June 29, Grinnell College hosted a six-day Presbyterian youth conference with 1,680 delegates from more than 40 states and 10 foreign countries. Among the 100-plus California delegates was one youth who had been infected at an earlier state conference in Davis, California. In turn, substantial numbers of the other attendees at the Grinnell conference fell ill (many were hospitalized), prompting officials to close the meeting early and send the delegates home.

No doubt these cases then transmitted the flu to Boy Scouts in several different locales, who subsequently assembled July 11-18 in Valley Forge, Pennsylvania. At the jamboree, 53,000 Boy Scouts were encamped, creating optimal conditions for exposure to the new strain of influenza. In August, the first community-wide outbreaks occurred in Louisiana and Mississippi. The numbers escalated in October and peaked in early November, very comparable to the 1918 epidemic. The vaccine could not be administered in time to interdict the new virus and its trail of illness.

In January 1976, an army recruit at Ft. Dix, New Jersey, collapsed during a field march and died shortly after. Other soldiers came down with the same illness. The New Jersey State Health Laboratory isolated

an influenza virus; other labs identified it as a strain of swine flu type influenza. In closed-door meetings, the Center for Disease Control (CDC) in Atlanta assessed the situation and then informed the media and the nation. Scientists and high-level federal officials decided on a controversial crash program of vaccine production followed by mass administration. Developing a vaccine got under way.

Meanwhile, public health professionals were searching for swine flu activity and possible seeding of the virus, as had occurred in the late spring and summer of 1918, and again in 1957. In April, CDC director David Sencer asked me to investigate a possible earlier swine flu infection of a Kellogg, Iowa, family whose son was among the ill at Ft. Dix. The young man had worked on a swine farm in Arkansas; while home for the holidays in late December 1975, he had decided to quit his farm job and enlist in the army. Unfortunately neither health history nor laboratory tests on the family members' blood corroborated a recent infection with swine influenza virus. Efforts in other states also failed to identify any swine flu activity excepting the predictable infection in pigs.

In August, the vaccine producers refused to release the vaccine unless the federal government assumed liability for any side effects; the producers' insurance carriers reasoned that an entirely new virus system posed too much risk for standard insurance coverage. As this was being debated, an outbreak of pneumonia at an American Legion convention in Philadelphia dominated national news; some speculated that swine influenza had arrived, prompting the U.S. Congress to hastily pass legislation for the federal government to assume liability for untoward effects of the vaccine.

The vaccination program cost \$135 million. In Iowa, 1,030,000 were vaccinated in less than two months, and before the usual flu season. But swine flu was not demonstrated anywhere nationally or globally, and the Philadelphia episode turned out to be a new bacterial disease called "Legionnaires disease." Unfortunately, too, some swine flu vaccine recipients (including some Iowans) developed Guillain-Barré Syndrome. This condition, usually developing a few weeks after a viral infection, is a distressing, flaccid paralysis of the lower body that ascends upward to the chest and arms. In some cases it requires several weeks for recovery and sometimes may be fatal.

For the past 36 years, with varying degrees of small changes or "drift," Hong Kong influenza has affected the human population. It originated in China and a pandemic followed in 1968. Like the 1918 Spanish flu virus, the Hong Kong flu virus has now entered swine

and was first detected in 1998 in North Carolina feeder pigs relocated to Iowa farms. The significance of this is that pigs can serve as a "mixing vessel," reassort viral components from humans and birds, and in turn shed a new virus potentially infecting humans. Presently the CDC is conducting surveillance studies in Iowa on swine farm workers, their families, and their hogs to monitor influenza activity and search for "recombinant" strains of flu virus that essentially represent hybrids of human, swine, and avian components.

The 1918 influenza outbreak, with its high attack rate and serious mortality levels, has continued to concern researchers. In 1997, Jeffrey Taubenberger and Ann Reid, at the Armed Forces Institute of Pathology, partially reconstructed the viral genome of the 1918 virus from archived tissue samples (preserved in formalin and sealed in wax) collected from deceased military victims in the pandemic.

Enjoying retirement in San Francisco, 72-year-old Johan Hultin read their progress reports. With modern virological techniques in mind, Hultin wrote to Taubenberger about repeating his 1951 expedition to Alaska. Taubenberger said he would welcome submission of specimens but had no funds for an expedition. Hultin called his travel agent; he would pay for it himself.

In August, permission was granted to again open the burial site in Brevig, Alaska. Hultin uncovered the remains of the eleventh body in the mass grave. "I sat on a pail—turned upside down—and looked at her," Hultin said. "Then I saw it. She was an obese woman; she had fat in her skin and around her organs and that served as a protection from the occasional short-term thawing of permafrost. Those on either side of her were not obese and they had decayed. I sat on the pail and saw this woman in a state of good preservation. And I knew that this was where the virus has got to come from, shedding light on the mysteries of 1918. I gave her a name. Lucy. I also thought of Lucy, *lux*, Latin for light. She would help Taubenberger shed light on that pandemic." Hultin constructed two new wooden crosses to replace the weathered crosses that had marked the burial site.

From Lucy's tissues, Taubenberger and Reid secured RNA from the virus, albeit inactivated but well-preserved enough to permit continuing study on the genome. How important is sequencing the genome from tissue of 1918 flu victims? First, the 1918 virus can be compared with other strains, and help establish evolutionary patterns in avian-like or mammalian-like strains. Second, sequencing enables "reverse engineering" of flu

and fabrication of new versions of flu virus. Researchers can learn how these viruses infect cells and sabotage the host's immune response as well as help develop prototypes for new vaccines. Without this capacity, detection and prevention of the next pandemic flu virus strain would be difficult, if not impossible.

Epidemiologists and medical historians have not set aside their anxieties over influenza. A brief scare occurred in April 2005. Authorities discovered that blind samples of flu virus, distributed to laboratories for testing staff proficiencies in identifying different strains, had accidentally included the 1957 influenza strain that dramatically affected a conference at Grinnell College that summer. This flu strain has not circulated since 1967; all persons born since that year would have been susceptible. Fortunately the error was detected and samples distributed earlier—including some in Iowa—were destroyed before infecting laboratory staffs, with subsequent spread to communities.

Since 1998, after eight decades of only classical swine influenza (H1N1) activity in pigs, two additional new strains of human influenza virus (H3N2) have been demonstrated in Iowa pigs. This observation coupled with the increased activity of avian influenza in Southeast Asia result in conditions that may enable reassortment of new strains of human influenza virus. Fifty human deaths were recorded from the most recent Asian outbreak (January 2004–April 2005).

Given that the world has not had a major "shift" since 1968, it would appear that a shift is due to occur, if not overdue. The increased sporadic cases of avian influenza virus in humans and the expansion of influenza strains now routinely found in pigs are worrisome indeed. Perhaps another Iowa scientist, or another recognition of early flu activity in Iowa, will provide vital insights and establish protocols to identify and interdict the next pandemic. ♦

Russell W. Currier served as the public health veterinarian at the Iowa Department of Public Health from 1975 to 2004, after six years with the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. He resides in Des Moines and has an avocational interest in medical health history.