

CAMPYLOBACTER

IMAGE: CENTERS FOR DISEASE CONTROL AND PREVENTION



DANGER AHEAD: THE RISE IN ANTIBIOTIC RESISTANCE

When Edward Oldfield III, MD, lectures second-year medical students, he tells them the great gift of antibiotics, lifesaving drugs of choice for 80 years, is disappearing.

You are destined, says the Professor of Internal Medicine, to practice in an era of limited choices because of the increasing resistance to the miracle drugs that quickly cured illnesses once considered fatal. “Some people,” he adds, “are talking about a post-antibiotic era. It’s going to be like back in the 1930s when we didn’t have anything.”

How serious is that? Consider this: When penicillin came on the market in the 1930s, it increased survival rates from pneumonia and blood infection from 10 percent to 90 percent. In those days, dying young from an infection was accepted, something that is rare today.

Back then, researchers and physicians knew that bacteria, which mutates rapidly, would eventually develop resistance to penicillin and the series of drugs that have followed. Alexander Fleming, who discovered penicillin, warned about the problem when he accepted his Nobel Prize in 1945.

Now, public health officials are speaking in apocalyptic terms to describe the threat. In 2013, Centers for Disease Control and Prevention (CDC) Director

Thomas Frieden, MD, and the United Kingdom’s Chief Medical Officer Sally Davies, MB ChB, MSc, warned of a coming “health nightmare” and a “catastrophic threat” because of the rise of a bacteria resistant to carbapenems, powerful antibiotics considered the last line of defense.

A landmark report issued last fall by the CDC conservatively estimated that two million Americans get infections resistant to antibiotics, and 23,000 of them die annually, more than from AIDS or Parkinson’s disease. A European Union report last year concluded that about 25,000 people there die every year from resistant bugs. According to the CDC, studies suggest antibiotic resistance is responsible for some \$20 billion direct health-care costs and another \$35 billion a year in lost productivity.

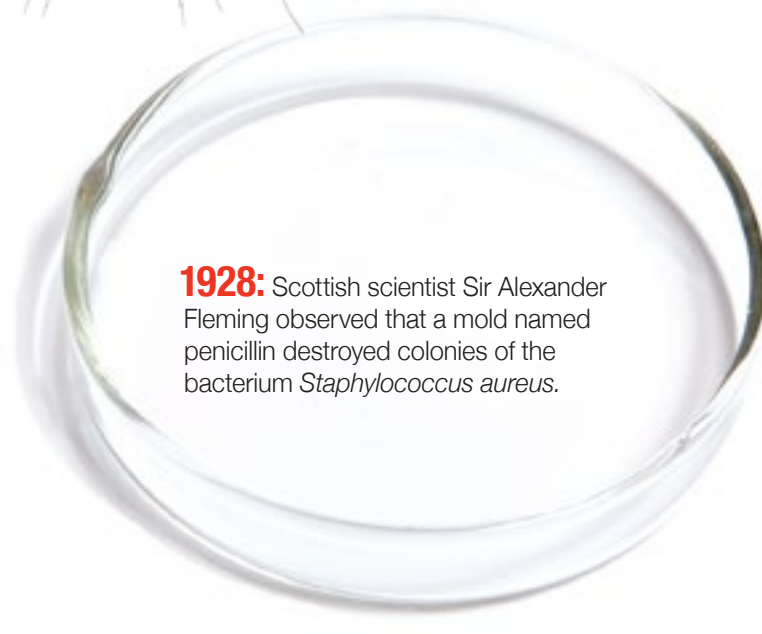
THE REGIONAL PICTURE

Dr. Oldfield says Hampton Roads hospitals have seen increasing numbers of infections resistant to powerful antibiotics, long considered the drugs of “last resort.” In one case, bacteria resistant to one of those antibiotics became resistant to a second, newer antibiotic during treatment. The patient eventually died from sepsis despite the use of multiple antibiotics.


Local hospitals have also experienced problems with infections that can be resistant to essentially all antibiotics and can survive for long periods on glass, plastic, metal and other materials in a hospital room. “We had two or three clusters of related infections,” Dr. Oldfield says, “and we had to be very aggressive in controlling them, but eventually we did control them.” To do so, infection control specialists strip the wax off the linoleum floors and remove the curtains in patient rooms, and then do a thorough cleaning.



PSEUDOMONAS AERUGINOSA



1928: Scottish scientist Sir Alexander Fleming observed that a mold named penicillin destroyed colonies of the bacterium *Staphylococcus aureus*.



1941: An Oxford policeman dying of infection was the first patient given penicillin, as a last resort. He died, but only because enough penicillin couldn't be produced to fully treat the infection.

While some local hospitals have dealt with adult patients infected with emerging resistant bacteria, Stephen Buescher, MD, Professor of Pediatrics, says he hasn't seen similar problems in children. "We've been pretty lucky," he says. "We've had only a handful of those children, and when they showed up, our lab was in the mode of looking for those problems. The lab at CHKD was able to identify the problem quickly and put patients in contact isolation to prevent the spread, and we were able to treat them with antibiotics we had available."

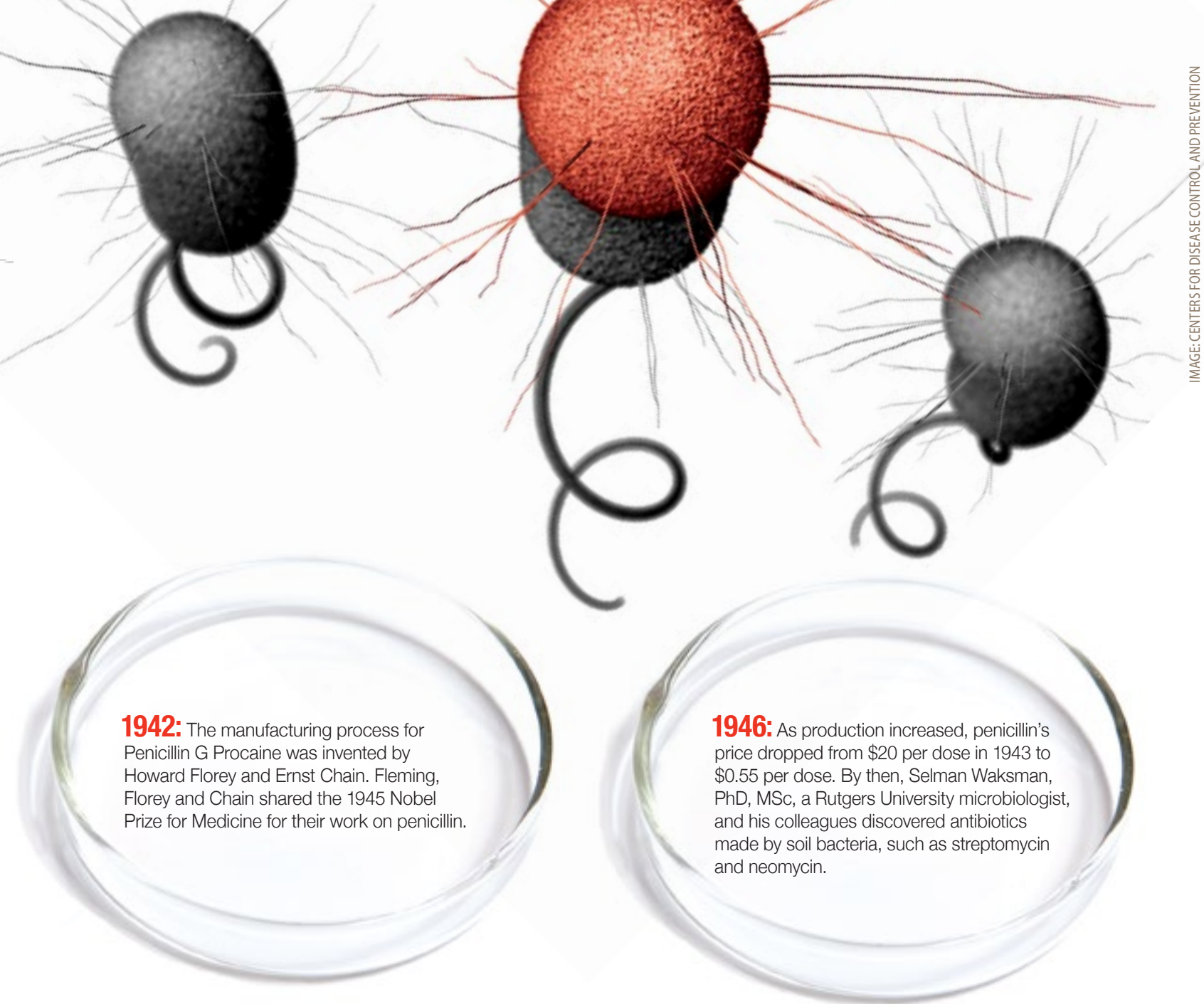
Still, he says, vigilance remains high. "At

the moment we're not hip deep in those kinds of problems. But we expect we're going to continuously interact with them in the future."

While the CDC report looks at antibiotic resistance nationally, Nancy Khardori, MD, Professor of Internal Medicine and an infectious disease specialist, says national data may not accurately reflect regional resistance patterns. In October, she and two students published the first survey of resistance in Hampton Roads using data from 12 regional hospitals. Dr. Khardori did a similar study in 2005 when she was the Chief of Infectious Diseases at Southern

Illinois University School of Medicine.

Overall, Hampton Roads has more antibiotic resistance now than what she found in Illinois eight years ago. The surveys shows that the minimum concentration of antibiotics to combat strains of *Staphylococcus aureus*, the most common hospital-acquired pathogen, is increasing. The researchers also found "serious shortcomings" in studies that tested bacteria for antibiotic resistance, because of variations in methodology, interpretation and reporting by local labs. By standardizing regional testing, local health-care officials can better interpret



1942: The manufacturing process for Penicillin G Procaine was invented by Howard Florey and Ernst Chain. Fleming, Florey and Chain shared the 1945 Nobel Prize for Medicine for their work on penicillin.

1946: As production increased, penicillin's price dropped from \$20 per dose in 1943 to \$0.55 per dose. By then, Selman Waksman, PhD, MSc, a Rutgers University microbiologist, and his colleagues discovered antibiotics made by soil bacteria, such as streptomycin and neomycin.

results and make changes to combat resistance.

"The danger and the risk are everywhere," Dr. Khardori says of the need for the survey. "What the regional study does is give us the exact scenario in the territory where we practice. Then we can handle things in a more targeted way."

NARROWING THE TARGET

When a patient is admitted to a hospital with a serious infection, it generally takes two to three days for lab tests to determine the cause and the best antibiotic. However, doctors can't wait for the results because

the infection will continue to grow. Therefore, often multiple antibiotics are prescribed initially while awaiting the results. That increases the potential that resistant strains will emerge.

By knowing what drugs are likely to be more effective, physicians can make a better first choice, Dr. Khardori says. "Constant vigilance looking at drug sensitivity is the only way we can give people the right antibiotic. If we wait for the laboratory to tell us what his or her bacteria looks like, we've lost the battle. What we should be telling our colleagues is these are the prevailing resistance patterns,

something that will help them choose the optimal antibiotic up front."

Dr. Oldfield and Dr. Khardori say the problem is the result of overusing antibiotics, one of the major issues cited in the CDC and EU reports. "The mantra for antibiotics is the more you use it, the faster you lose it," Dr. Oldfield says, noting increased usage means resistant strains develop faster. "It seems like the bacteria are always one step ahead of us in anything that we try to do. They mutate so quickly."

The CDC report concluded that about half the antibiotics prescriptions written in the United States are inappropriate.



SALMONELLA TYPHI

1947: Four years after drug companies began mass-producing penicillin, microbes that could resist it began appearing.

1940s to 1970: During this golden age of antibiotics, 10 classes of antibiotics, each with different targets, were identified, according to the *New England Journal of Medicine*.

Further fueling resistance is the use of antibiotics in animals. About 80 percent of the antibiotics used in the U.S. are given to livestock, often to promote growth in healthy animals, something that has been outlawed in Europe. Drug-resistant bacteria get into humans through meat and feces and can be spread through unclean hands or surfaces.

TACKLING THE CHALLENGE

Dr. Khardori says she will update the regional resistance surveillance annually. Creating a partnership among local health systems to track resistant germs could result in a reduction of resistance, she adds.

“Twenty years ago, we still had hope,” she says. “We still had something in our pocket for when we would get down the

line, and we would be able to overcome those bacteria that have become resistant. Now, in many respects, we’re at the end of the line. There is not much in the pipeline (developing new drugs). That is the major difference between then and now.”


Another issue is that new antibiotics are expensive to create. According to a World Health Organization report, drug companies are more focused on developing medications to treat long-term conditions rather than those that cure patients in a matter of days.

“We live in a bacterial world where we will never stay ahead of the resistant mutation curve,” Dr. Oldfield adds. “A test of our resilience is how far behind the curve we allow ourselves to fall.” With few drug companies looking to discover new antibiotics, “we are allowing ourselves to fall

way behind the power curve.”

Patients, he says, should make their doctors justify prescribing antibiotics; physicians should take the time to educate patients about viruses, which don’t respond to antibiotics, and side effects of certain antibiotics, which can include colitis, tendon ruptures and retinal detachment.

Dr. Oldfield ends his lecture on antibiotic resistance with a reminder: “Microbes swim in the evolutionary stream, and they swim much faster than we do. Bacteria reproduce every 30 minutes. For them, a millennium is compressed into a fortnight. Microbes were here learning every trick of survival two billion years before humans arrived. And it is likely they will be here two billion years after we depart.” □



2006: A study in *Nature Biotechnology* found that since 1998, the Food and Drug Administration had approved only four antibiotics.

2013: A CDC report noted that the number of new antibiotics developed and approved has steadily decreased in the past three decades and that only one new antibiotic was approved in the previous three years.