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LOS ANGELES TIMES

Spreading a New Idea on Disease Mounting evidence may link viruses and bacteria to everything from gallstones to Alzheimer's.

By Thomas H. Maugh II. Times Medical Writer

Even Chronic Diseases Are Being Linked to Viruses and Bacteria

The newspaper articles on the following pages from the Los Angeles Times on April 22, 1999 link pathogens such as viruses and bacteria to diseases ranging from ulcers to cancer.

Similar information has been printed in several magazines and newspapers over the last few months.

Why shouldn't the headlines read?

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Spreading a New Idea on Disease
Mounting evidence may link viruses and bacteria to everything from gallstones to Alzheimer's.
By Thomas H. Maugh II. Times Medical Writer

Ignaz Semmeiweis was ahead of his time. Working at Vienna General Hospital in the 1850's, the Hungarian physician was one of the first to adopt the idea that germs cause disease. Semmeiweiss noted that doctors would perform autopsies in the hospital's basement, then care for healthy pregnant women without cleaning their hands. Many of the women developed fatal fevers, and Semmelweis reasoned that the doctors were transferring some kind of infectious agent from the corpses to the women.

Contagion was a radical idea at a time when illness was thought to be caused by bad blood or other mysterious forces, and Semmelweis was ridiculed for his ideas.

Today, we know that most acute diseases are caused by bacteria, viruses and other agents.

Now, a growing number of latter-day Semmelweises are advocating an even more radical notion-that viruses and bacteria play a major role in many chronic diseases where infection has never been suspected.

At a time when much research focuses on the genetic underpinnings of disease, researchers say, it is time to take a fresh look at how an old foe- infections-can interact with genes to produce chronic disease.

If they are right, physicians might soon have new antibiotic and antiviral weapons to add to their arsenal for treating heart disease, Alzheimer's, kidney stones, gallstones and a variety of other chronic conditions. It might even be possible to develop vaccines to prevent some of these conditions.

Already, bacteria and viruses have been firmly linked to ulcers, liver cancer, cervical cancer, leukemia and Kaposi's sarcoma.

Strong evidence is also unfolding for other diseases: * Epidemiologists have found that a majority of heart disease patients have been infected with a common bacterium and Canadian researchers recently reported a mechanism by which it could trigger heart disease. Some researchers suspect that as many as 80% of all cases of heart disease are linked to infections.

* Pennsylvania scientists have found the same bacterium in the brains of patients with Alzheimer's disease.

* Finnish biologists have strong evidence that a previously unrecognised bacterium can produce kidney stones.

* More tentatively, other researchers have linked infections to a broad spectrum of diseases, ranging from Crohn's disease and irritable bowel syndrome to obsessive compulsive disorder, schizophrenia, multiple sclerosis and arthritis (see box).

Studies Focusing on Antibiotics

The links to infection raise "the prospects for treating and preventing these chronic diseases" said biologist Paul Ewald of Amherst University. "If it's a bacterium that is susceptible to a wide range of antibiotics, that is incredibly encouraging."

Already, some small studies have suggested that antibiotics might prevent heart attack and three large clinical trials enrolling nearly 8,000 people have begun or are beginning. Neurologists are also preparing a trial using antibiotics to treat Alzheimer's disease, and it is likely that trials for other chronic diseases are on the horizon.

That doesn't mean you are going to be able to throw away your blood-pressure medicine or eat more fatty foods. Infections are just one more risk factor to add to the complex equations determining risk. Some researchers believe, for example, that controlling infections might have the same benefit for heart disease patients as lowering cholesterol.

"This to an idea whose time has come," said Dr. W. Ian Lipkin of the UC Irvine School of Medicine. "We have been tracking [this] for many years, and it is finally achieving some respectability."

The new discoveries are occurring in part because some researchers are choosing to look for links to infectious agents. But more important, perhaps, has been the development of sophisticated DNA-based techniques for identifying the presence of trace quantities of bacteria or viruses.

Polymerise chain reaction (PCR) technology, widely heralded for its use in providing genetic fingerprints of humans, can be used to fish out the genetic fingerprints of viruses or bacteria in human tissue, even though the organisms are present only in minute quantities.

"If [the viruses or bacteria] were causing disease in an obvious way," Ewald adds, "we would have seen it long ago. It shouldn't surprise us.. that every new one we find tends to be a little more cryptic."

The godfather of the new movement is Dr. Barry J. Marshall who was at the Royal Perth Hospital in Australia in 1981 when he and Dr. J. Robin Warren began studying an unidentified spiral bacterium that they observed in stomach linings.

After several years of study, they concluded that the bacterium, named Helicobacter pylori is the cause of most ulcers not associated with over-ingestion of painkillers-an idea that the vast majority of physicians considered laughable at the time. They also found that eradicating the bacteria, which is found in the stomachs of a third of Americans, cured the ulcers.

But it was not until Marshall himself, now at the University of Virginia, swallowed a vial of H. pylori and developed a painful case of gastritis that other physicians began to be convinced. “That surprised people,” Ewald said.

“At least two generations of doctors were trained to think of ulcers as being caused by too much stomach acid,” said Dr. Monty Boderiheimer of the Long Island Jewish Medical Centre in

DISEASE: Infections’ Role Studied New Hyde Park, N.Y. “But now we know differently and don’t treat ulcers as too much acid. We treat the infection.” Current guidelines, in fact, call for the use of two antibiotics plus an anti-acid drug, but many doctors have not yet gotten the message. A recent Colorado study showed that 46% of patients seeking treatment for ulcers are never tested for H. pylori by their physicians. Subsequent studies have also shown a strong link between the bacterium and stomach cancer.

Some researchers have also found tentative links between H. pylori and heart disease, the No. I killer in the United States. Others think the villain might be either cytomegalovirus, a herpes virus, or even the bacteria in dental plaque.

But the strongest evidence implicates another bug, called Chlamydia pneumonia, in heart disease. Discovered in the 1980s, C. pneumonia is now known to be widespread in the environment, causing, for example, at least 10% of all cases of pneumonia. It is also a close relative of Chlamydia trachomatis the most common cause of sexually transmitted disease in this country.

The idea that bacteria and viruses can damage the heart is not farfetched. The streptococcal bacteria that cause rheumatic fever also attack the heart, causing lingering damage. Several viruses attack the heart directly, causing myocarditis, which is often fatal.

Staphylococcal and streptococcal bacteria have also recently been shown to cause Kawasaki syndrome, a childhood disease that is marked by severe heart problems. If infectious agents can cause acute heart disease, some researchers reason, it is not a big leap to the idea that they can cause chronic disease as well.

Beginning in the late 1980’s researchers such as Dr. J. Thomas Grayston of the University of Washington began finding high levels of antibodies against C. Pneumonia in the blood of patients with heart disease. Few paid much attention to such findings until 1995, when Dr. James Summersgill and his colleagues at the

University of Louisville found the same bacterium in the atherosclerotic plaques that blocked blood vessels taken from a patient undergoing bypass surgery. Researchers have since found the bacterium in the blood vessels of virtually every heart disease patient studied, but never in vessels from healthy patients.

But just because the bacterium is at the scene of a crime doesn’t mean it is necessarily a criminal. It may simply find plaque an ideal environment in which to grow. “Chlamydia Pneumonia may just be an innocent bystander in diseased blood vessels,” said Dr. John Danesh of Oxford University. Nevertheless, proponents

like Grayston think there are good reasons to suspect it. Scientists have long known that atherosclerosis is an inflammatory disease that affects vessels throughout the body, but particularly those supporting the heart and brain. Heart disease develops when our immune systems mobilise to remove fat, cholesterol and other irritants from vessel walls. As immune cells called macrophages burrow into the arterial walls to gobble up foreign material, they can set off a vicious cycle of irritation and scarring.

Germ Warfare Grayston and others suspect that C. pneumonia exacerbates that inflammatory process, or may even provoke it in the first place. Recently, Dr. Josef Penninger and his colleagues at the Ontario Cancer Institute in Toronto showed how that could occur. They reported that the surfaces of three strains of chlamydia carry a protein very similar to a protein found only in heart tissue. When they injected the chlamydia proteins into mice, the mice developed heart disease. The question then is: If the bacterium contributes to the development of heart disease, will eradicating it reduce risk? In February, Dr. Hershel Jick and his colleagues at Boston University Medical Centre reported that patients who took tetracycline or quinolones-antibiotics known to kill C. pneumonia - were less likely to have heart attacks than people who took other antibiotics or no antibiotics. Other small studies have found similar results.

To test this idea on a larger scale, Grayston and Dr. P.K. Shah at Cedars-Sinai Medical Centre in Los Angeles have independently begun testing the anti-chlamydia antibiotic Zitliromax against a placebo to determine if the drug reduces heart attack risk. Zithromax manufacturer Pfizer Inc. is also conducting a large trial.

Perhaps even more surprising than C. pneumonia's link to heart disease is a potential link to Alzheimer's, a devastating neurological disease that afflicts more than 4 million Americans. Dr. Brian J. Balin of the Philadelphia College of Osteopathic Medicine and Dr. Alan P. Hudson of the Wayne State School of Medicine in Detroit reported at a November meeting of the Society for Neuroscience that they found traces of C. pneumonia in the brains of 17 of 19 people who died of Alzheimer's disease, but in only one of 18 people who died from other causes.

They have since found it in 10 more Alzheimer's victims, Balin said in a telephone interview. "We wanted to be clear about what we found, so we used seven different techniques to identify it," he said.

The presence of inflammation in the brain triggered by an immune attack of the bacterium might explain studies suggesting that aspirin and other anti-inflammatory drugs delay the progression of Alzheimer's, he said. Balin also noted that some Alzheimer's patients have told him that their cognitive ability improved while they were taking antibiotics for other conditions.

That might be giving us a clue," he said. He plans to conduct a clinical trial to see if antibiotics can slow the progression of Alzheimer's in its early stages.

Triggering an immune attack may not be the only way that bacteria cause chronic disease. Other recent studies suggest that certain bacteria can act like the proverbial grain of sand that triggers the formation of a pearl in an oyster. But in these studies, the bacteria produce kidney stones and gallstones. Biochemist E Olavi Kajander of the

DISEASE: NeW Theory University of Kuopio in Finland has spent the last decade studying new strains of bacteria that he calls nanobacteria because they are extremely small, some as small as a virus. The nanobacteria have been unknown in the past, he said, because they are so small and because they are extremely difficult to grow in the laboratory. But he has found that 5% of the Finnish population has

antibodies against nanobacteria, indicating that those people have been infected at some time. Last July, Kajander reported that every one of 30 kidney stones he and his colleagues took from various patients had nanobacteria in their centres. His lab

had previously shown that the bacteria cloak themselves in a shell of crystalline minerals. He speculates that such bacteria, which live in urine, act like a seed around which calcium and other minerals can grow to form a large stone. “I think it is the first real theory as to what” is the seed in kidney stones, said Dr. Leroy M. Nyberg of the National Institute of Diabetes and Digestive and Kidney Diseases. Dr. Phillip B. Hylemon of the Medical College of Virginia suspects that more common bacteria, clostridia and eubacteria, may play a similar role in gallstones. He found that gallstone patients have 100 to 1,000 times as many of these bacteria in their intestines as do healthy people.

He also reported last year that giving such patients antibiotics reduced their levels of bile-a bitter fluid produced by the liver to aid digestion-below the threshold necessary to make gallstones. Many experts believe that researchers have just barely begun to scratch the surface in looking for dangerous infectious agents. “My gut feeling is that the more we look, the more we are going to find microorganisms that have taken up residence in the human body,” said biologist Hal B. Nash of Western Wyoming College. “Some may not be doing any harm, but others may be doing quite a bit.”

Spread by Germs Several chronic diseases once thought to be caused solely by genes and lifestyle have now been shown to be caused, at least in part, by infectious agents. Others have been tentatively linked to such agents as well.