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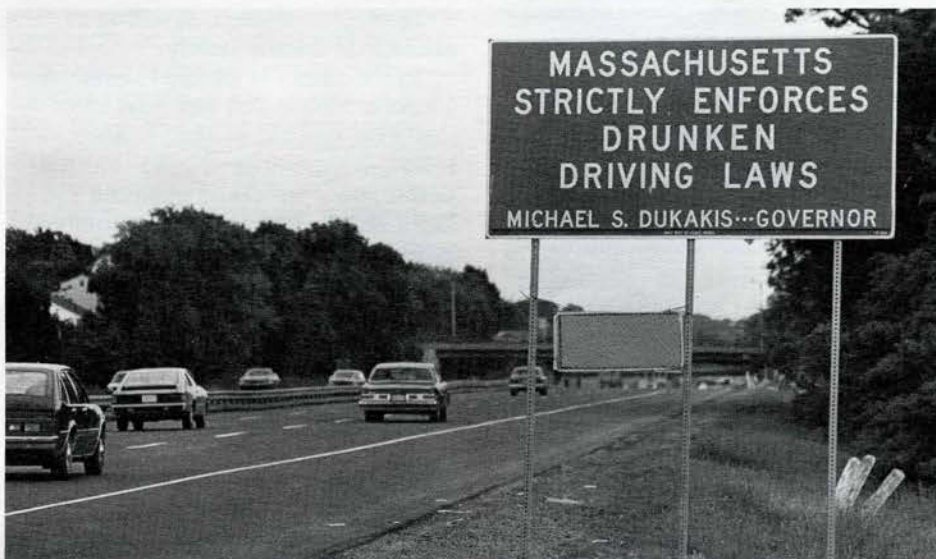
Is aspirin a powerful weapon against cardiovascular disease? Studies by a BUSM research team headed by Daniel Deykin, M.D., aim to answer this question, which has been the subject of intense debate within the medical community. See story on page 3.

BUSM researchers seek to develop vaccine to protect against gonorrhea

Each year there are between two and three million new cases of gonorrhea in the United States. Not all of the cases take the form of sexually transmitted diseases that most people think of when they hear the term.

Neisseria gonorrhoeae, as the bacteria that cause gonorrhea are called, also is one of the major causes of pelvic inflammatory disease, a condition that often strikes women in their reproductive years, resulting in infertility in 15 percent of the cases. The bacteria also cause disseminated gonorrhea, a less common blood-borne form of the disease that can produce painful and infected joints, skin lesions and sometimes infection of the heart valves.

While all of these conditions generally can be treated with penicillin, increasingly there are strains emerging that are resistant to the drug. And, for example, in the case of pelvic inflammatory disease, even when the antibiotics eradicate the infection, the damage to the female's reproductive tract, which frequently results from complications of the disease, may be permanent. In addition, one of the challenging factors involved in treating the disease is that often both males and females appear to have no symptoms or
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The effectiveness of more rigid drunk-driving laws in Maine and Massachusetts is being examined by researchers at BUSM.

Are drunk-driving laws saving lives? BUSM research team seeks answers

On a recent winter afternoon, as a 13-year-old Rhode Island boy was walking to a sporting goods store near his home, he was struck by a car. Police charged the driver of the car with driving under the influence of alcohol. The boy, who was knocked 90 feet away from the auto, died instantly.

This teen-ager is one of between 16,000 and 30,000 people who die each year in car accidents involving drunk drivers. Officials estimate that one-third of all drivers in fatal crashes have blood alcohol levels of at least .10 at the time of the acci-

dent (the equivalent of about five drinks on an empty stomach).

In an attempt to reduce these alcohol-related tragedies, and under tremendous pressure from such lobbying groups as Mothers Against Drunk Driving and Remove Intoxicated Drivers, 34 states in the past two years have passed tough laws to deter drunk driving.

Many questions now are being raised about the effectiveness of these laws. Do people in states with strict drunk-driving legislation actually drive less after drinking? Are there
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Drunk-driving...*continued from page 1*

fewer alcohol-related accidents in these states?

In an attempt to determine if these laws actually are saving lives and if the laws have a sustained effect on drunk-driving, researchers at the School of Public Health at Boston University School of Medicine are conducting a concentrated study on the effects of drunk-driving legislation passed in Maine and Massachusetts.

Originally, when the study began in 1981, SPH researchers planned to concentrate only on the drunk-driving legislation passed in Maine, which when enacted in 1981, was dubbed "the toughest drunk-driving law in the nation." They planned to use Massachusetts, which at that time had less strict drunk-driving laws, as a state with which to measure the results of the Maine law.

With the recent passage of more strict Massachusetts legislation, the study has been expanded to evaluate the effectiveness of the laws in both states, using other states in New England as the control.

While the drunk-driving laws in Massachusetts and Maine are similar in some respects, they differ significantly in others. The Massachusetts law, passed in 1982, concentrates on increasing drunk-driving penalties, particularly for repeat offenders.

Maine's legislators both increased the penalties and made them mandatory, but also took steps to expedite the judicial process and increase the likelihood of conviction. These steps include a provision making operating under the influence of alcohol a civil offense, requiring the state only to establish a preponderance of evidence to convict drunk drivers, instead of proving guilt beyond a reasonable doubt as required in other states. Also, the legislation made it illegal to drive with a blood-alcohol level of .10 or higher. Previously, blood-alcohol levels were presumpt-

tive evidence that allowed offenders to contest this charge in court.

Officials of both states hoped these changes would reduce plea bargaining, would force more speedy trials and would act as a clear deterrent to the potential drunk-driver.

Before Maine's law went into effect, the drunk-driving problem there was similar to that in virtually every other state in the nation. About 60 percent of all Maine traffic accidents were alcohol-related, resulting in about 200 deaths yearly.

"In the summer of 1981, when we became aware that this new law might be passed in Maine, we contacted the governor's office there to determine if we could evaluate the law's effect. They were extremely interested," said Ralph W. Hingson, Sc.D., an associate professor of public health (social and behavioral sciences) at SPH and principal investigator of the study.

The researchers then devised a survey to be used in 1,000 random telephone interviews in Maine. They also planned 1,000 interviews with residents in Massachusetts, which at the time lacked the more strict drunk-driving laws, to use as a comparison group. The researchers decided to conduct the survey once a year for three years to determine whether the new law would have a sustained effect.

The survey included such questions as:

- "How likely do you think it is that drunk drivers would be arrested in your state?"
- "How often would these drunk drivers be convicted?"
- "How often do you drive after drinking?"

Other factors being investigated by Hingson's team include the statistics in these states on drunk-driving arrests and convictions, fatal accidents and deaths due to accidents.

Researchers who in the past have studied the effects of drunk-driving laws are "very skeptical about the ability of the drunk-driving laws to

make a difference" over longer periods of time, according to Hingson.

A 1981 report by the Insurance Institute for Highway Safety concluded: "None of the countermeasure approaches devised and implemented (by states) to deter these drivers has been found by competent research to have a permanent influence on reducing deaths resulting from crashes by drunk-drivers."

In addition, a recent study by Hingson's research team showed that the 1981 legal drinking age change from 18 to 20 in Massachusetts has had only modest effects on the drinking and driving behavior of the state's teen-agers. The two-year study showed that, in comparison to teen-agers in New York state, there was no decline in overall fatal crashes among 16- to 19-year-olds in Massachusetts.

Because Maine's law went into effect only weeks after BUSM researchers became involved in the study in the summer of 1981, the team had to work quickly to collect their first set of survey data to use as a pre-law change baseline.

Working together with Maine officials, the team was able to complete their calls that August.

The second survey blitz was completed in the summer of 1982, and the researchers are conducting the questioning again this summer.

While the interviews began merely days after the research proposal was hatched, funding for the project came much more slowly.

In August 1981, Maine officials donated a starter fund with which the researchers were able to begin their first Maine survey.

While the researchers waited for grants from other organizations to continue their work, BUSM Dean John I. Sandson and Norman A. Scotch, Ph.D., director of SPH and chairman of the Department of Socio-medical Sciences and Community Medicine, donated some School money to keep the project alive.

"The School of Medicine and the

School of Public Health went out on a limb for us. Drs. Sandson and Scotch felt that this was an important project and trusted that we would eventually get the funds to complete it. I was very impressed with their willingness to do that," said Hingson.

Finally by June of last year, the National Institute of Alcoholism and Alcohol Abuse; the Milbank Fund, a private philanthropic institution; the U.S. Department of Transportation, and the Commonwealth Fund all contributed to the project.

Hingson currently is collecting data from a control group made up of other New England states to compare with Massachusetts residents' drunk-driving perceptions and statistics. He also is working to gain additional funding to extend the study to evaluate the Massachusetts law over time.

"We are providing ongoing information to officials in the states involved in our study who are interested in what impact their law is having on public perceptions of drivers," said Hingson.

In addition to Hingson and Scotch, other researchers involved in the project are: Allan R. Meyers, Ph.D., an associate director of SPH and an assistant professor of public health (health systems); Thomas W. Mangione, Ph.D., a SPH adjunct associate professor of public health (epidemiology and biostatistics); David Kovenock, Ph.D., director of the Social Science Research Institute at the University of Maine in Orono; Timothy Heeren, B.A., a SPH instructor of public health (epidemiology and biostatistics); and Suzzette Morelock, a SPH research assistant.

—Paul D. Vaskas

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Role of aspirin in heart disease investigated by BUSM research team

In recent years, studies suggesting that aspirin might be a potent weapon against cardiovascular disease have stirred intense public interest.

It isn't difficult to imagine why that idea has elicited interest. Here is an inexpensive drug that is available at every corner grocery or drugstore and that has been around long enough for the medical community to conclude with considerable certainty that for most people it has no major side effects (although it may cause gastrointestinal bleeding in some people).

Unfortunately, though, the matter of aspirin's effectiveness against cardiovascular disease is by no means resolved. In fact, the issue still is being hotly debated within the medical community.

At this point, there is no way of knowing when the debate will be concluded and what its outcome will be. But research being carried out by investigators at Boston University

School of Medicine shows strong promise of helping to bring about an early resolution of the aspirin issue.

The research, which is supported with funds from the National Heart, Lung and Blood Institute and the Veterans Administration, is being carried out under the direction of Daniel Deykin, M.D. Deykin is the Maurice B. Strauss Professor of Medicine at BUSM and Tufts University School of Medicine, and is chief of medicine at the Boston Veterans Administration Medical Center, which serves as a teaching site for both medical schools.

Deykin, who oversees a wide variety of research related to the body's circulatory system, said that recent findings about aspirin's behavior in the bloodstream have helped to bring the dispute over the drug into better focus.

The key factor, said Deykin, is the effect that aspirin has on both the platelets—those tiny elements in the blood that are the main components



Daniel Deykin, M.D., seeks clues to understanding aspirin's role in heart disease.

of blood clots—and the blood vessels.

“Aspirin causes platelets to become less active, and if you’re trying to prevent the platelet buildups that can lead to coronary occlusion or to a stroke, that’s good. But the aspirin also seems to make changes in the blood vessel walls that may not be so good,” said Deykin.

Ironically, both kinds of interactions result from the fact that aspirin chemically modifies a certain type of enzyme, thereby preventing the enzyme from carrying out its normal function as a catalyst.

In the platelets, this enzyme’s role is to trigger a process that results in the production of a substance that tends to make the platelets “sticky.” This substance, called thromboxane, can cause platelets to build up on a blood vessel wall, said Joseph A. Jakubowski, Ph.D., a research associate at BUSM and one of Deykin’s collaborators. If such buildups become large enough, he added, the result may be a coronary occlusion.

In the cells that line blood vessel walls, however, this same enzyme leads to the production of another substance called prostacyclin, which tends to keep platelets from collecting on the vessel walls.

If there were no more to the issue than that, the case for aspirin’s value as a protective agent against cardiovascular disease might look weak.

A key question, however, said Deykin, is whether there is some dose level at which aspirin will “suppress activity in the platelets while largely sparing the blood vessels where the thrombi—the platelet buildups—commonly occur.” In fact, Deykin and his associates have uncovered convincing evidence that such a dosage does exist.

“In a series of animal experiments,” said Jakubowski, “we found that if we used an aspirin dose of one milligram per kilogram of body weight—which would be the equivalent of an adult taking one baby aspirin—the production of thromboxane

by platelets is strongly suppressed.”

On the other hand, he went on, aspirin at that dosage did not suppress the production of prostacyclin in the animals’ arterial walls.

According to Deykin, the next step in trying to pursue the low-dosage hypothesis will be another series of experiments involving primates, to be carried out in collaboration with William Hollander, M.D., a professor of medicine and biochemistry at BUSM. In the experiments, which are expected to take approximately a year to conduct, the animals will be fed a diet that predisposes them to atherosclerosis, and some will be given aspirin at low doses. Then the groups of animals will be monitored to see if the low-dose aspirin helps to prevent the platelet buildups that are often preludes to coronary occlusion and stroke.

Deykin cautioned, however, that even if the project yields the positive results that the preliminary research seems to point to, it still will not provide definitive indications on whether a low-dose aspirin regimen also would work in humans. However, he said, such results would provide a strong inducement to move on to clinical trials involving patients at serious risk of developing coronary disease.

Another research avenue being pursued by Deykin and his associates is in providing new information about some of the basic mechanisms underlying the onset of arterial disease.

Several years ago, said Deykin, he and his fellow investigators noted that arachidonic acid—a fatty acid that is one of the key factors in the process leading to the buildup of platelets in blood vessels—is highly concentrated in certain components of platelets.

“While looking for the enzymes that might account for this accumulation of arachidonic acid,” he said, “we have found a new enzyme, one that works by a method that seems to be different from any other

platelet enzyme.”

In most interactions in the platelet between enzymes and arachidonic acid, the acid first is freed from its storage place within the platelets; once freed, other enzymes go to work on it to produce a variety of substances related to the functions of the platelets—including thromboxane, which makes platelets stick to the blood vessels and to one another.

This new enzyme, called arachidonoyl-transacylase, however, seems to transfer the arachidonic acid to certain components of the platelet without the acid’s first having to be freed from those portions of the platelets where it is normally stored.

“That’s a new kind of process,” said Ruth M. Kramer, Ph.D., an assistant professor of biochemistry at BUSM and another of Deykin’s collaborators. “Another fascinating thing about this enzyme is that it’s highly specific. We’ve found in some of our lab work that it can discriminate between arachidonic acid and compounds that, chemically, are virtually identical.”

Such interesting properties, said Deykin, do not yet shed much light on such questions as what the enzyme’s role is in making the body prone to coronary disease. He added, however, that the preliminary findings are intriguing enough to make the enzyme well worth further scrutiny.

“Now that we’ve described how it works,” he said, “we’re going to try to purify it, to identify its location within the platelets and elsewhere, and to find out how it is regulated.”

—Richard P. Anthony

Suggested Further Readings

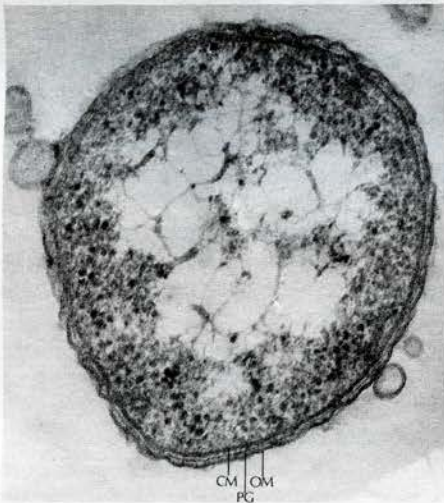
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Gonorrhea vaccine... continued from page 1

don't recognize symptoms that they might have, and the spread of the disease continues.

The many challenges of diagnosing, treating and preventing infections caused by the different strains of *Neisseria gonorrhoeae* are the focus of research being conducted by Boston University School of Medicine faculty member Peter A. Rice, M.D., as he and his research team seek to develop a vaccine that could be used to immunize humans against the harmful effects of gonorrhea-causing bacteria, also called gonococci. Rice is an associate professor of medicine at the School and director of the Clinical Immunology Laboratory at Boston City Hospital. His work in gonorrhea, which is conducted in the Maxwell Finland Laboratories for Infectious Diseases, is supported by the National Institutes of Health, although he is seeking additional funding.

For seven years, Rice and his col-



This electron micrograph shows a *Neisseria gonorrhoeae* cell. The cell has been stained to show the components of the cell wall: the inner wall, or cytoplasmic membrane (C.M.); the outer membrane (O.M.); and peptidoglycan (P.G.), the substance that lies between the two walls. (Photo by Floyd Craft)

leagues have been studying the gonococcal organism at the immunochemical level in an effort to understand how gonococci interact with the host (or human body), what changes take place to cause the bacteria to produce different manifestations of the disease and how the human body interacts uniquely with the different strains.

The researchers are, in turn, putting this basic research to practical use in other ongoing laboratory experiments as they work to develop methods that would be useful in rapid diagnosis of the disease and a vaccine or group of vaccines capable of immunizing humans against one or more of the diseases caused by *Neisseria gonorrhoeae*. It is the researchers' hope that humans could be protected, if not from all forms of gonorrhea, at least from those that are invasive and result in clinically more severe infection.

"We are trying to pinpoint what antigens (or antibody-provoking substances) would be most useful for immunization," Rice said. "And, while vaccine trials in humans currently are being performed by other research teams, the antigens that are being employed by those investigators have been chosen because they may enable human hosts to produce antibodies in their genital secretions that will prevent the organism from securing a foothold. Our attention presently is focused on a vaccine that will protect humans from invasion by gonococci beyond the genital surfaces."

Rice also is conducting similar investigations to test the feasibility of developing an immunization program to protect humans against non-typeable *Haemophilus influenzae* (NTH), which is a major contributor to the 20 million cases of otitis media or middle ear infections that occur each year, primarily in children. This bacteria also causes sinusitis in adults and children, and pneumonia, especially in the elderly or hospitalized. Rice is conducting the influenza



The challenge of preventing infections caused by gonococci is one focus of research being conducted by Peter A. Rice, M.D., shown above with laboratory technologist Sunita Gulati.

studies in cooperation with Steven I. Pelton, M.D., an associate professor of pediatrics at the School and associate director of pediatrics at Boston City Hospital, and Aubrey Milunsky, M.B.Ch., professor of pediatrics and director of the Department of Pediatrics' Section on Medical Genetics.

One of the key elements in the development of the gonorrhea vaccine is a group of antigens known as lipopolysaccharides (LPS).

"An LPS vaccine, as it stands now, would be quite toxic—people might get sicker from the vaccine than from some forms of the infection. But, we are preparing a derivative of the substance that would be less toxic," Rice said.

Lipopolysaccharides are one of the major structures found in the outer membranes of many bacteria, including gonococci. In laboratory tests, the researchers have found that LPS can provoke the production of an antibody in humans that assists in killing the invasive types of gonococcal organisms.

"The evidence, indirect as it is at

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this time, suggests that these antibodies, which are directed against LPS antigens, might be useful in protecting humans against invasive forms of the infection if, in fact, the antibody can effectively recognize the organism and, together with a group of other blood components called complement, kill it directly or facilitate its killing by the host's white blood cells before the gonococci have a chance to multiply and spread," Rice said.

The researchers also are working to detoxify LPS antigens so that these antigens would be more suitable for human use, while still preserving their antibody-producing properties. "We also want to determine what mix of antigens might be needed to stimulate antibodies effective against a broad array of organisms," Rice said.

Another class of antigens under study by Rice and his research team is known as outer membrane proteins. One study conducted by the researchers indicates that naturally occurring antibodies directed against these antigens in normal healthy individuals may, in fact, protect the gonococcal organism and be a liability to the host. These antibodies prevent the host from being able to kill the invading organism by screening out or blocking access of the killing antibodies to their binding sites on the surface of the organism—in other words, the host turns on itself. "We think these blocking antibodies might be most important in individuals who have the bacteremic or disseminated form of the disease," Rice explained.

"Another of the interesting aspects of the gonococcus is that it's extremely adaptable to humans. It has employed many ploys to try to trick humans into thinking it's not there, or it uses the humans' own immunologic mechanisms to protect it instead of protecting the human," he added.

Rice's studies of the immunological differences between the various strains of gonorrhea have turned up many interesting findings that are useful tools in helping advance the immunization efforts.

"What we know is that strains that cause pelvic inflammatory disease are often very serum-sensitive (they are killed by normal human serum) while strains that reach the bloodstream are serum-resistant," Rice said. "While we don't fully understand what causes an organism to be serum-sensitive or serum-resistant, we believe a serum-sensitive organism is capable of producing a local inflammatory response much more readily than a serum-resistant organism."

For example, he continued, the strains that cause pelvic inflammatory disease probably have the potential of causing much more inflammation by stimulating inflammatory mechanisms in the genital secretions

and tissues they affect than do the gonococcal strains that cause the disseminated form of the disease. "Fewer than 30 percent of individuals who have the disseminated or blood-borne form of the disease have any symptoms at the original site of infection, usually a genital site," Rice said.

"We have observed an immunologic phenomenon and have dissected it to learn more about how the host interacts with particular antigens present on gonococci," Rice said. "With this information, we hope to understand not only what the immunologic mechanisms are and how they interact with the organism's antigens, but we also hope to define these antigens and gain insight into how they might be useful as vaccines."

—Marjorie H. Dwyer

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