NEWS

THE UNIVERSITY OF TEXAS
(SOUTHWESTERN)
MEDICAL SCHOOL AT DALLAS

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DALLAS--In a labyrinth of laboratory tubes, flasks and cylinders, scientists here are producing a key ingredient in a coordinated worldwide assault on cholera, the age-old diarrheal scourge which sprang to life anew this summer in two dozen countries.

Concentrated amounts of purified cholera toxin, isolated after a painstaking five-year search, are being supplied regularly by researchers at The University of Texas (Southwestern) Medical School to other laboratories around the world engaged in stepped-up studies of the disease, says Dr. Richard A. Finkelstein, director of the Dallas research.

The toxin is a poisonous protein given off by the tiny but potent cholera bacteria, which triggers the infectious malady that has brought misery to millions and--despite medicine's relentless efforts--still brings death to thousands.

The Dallas-produced material has been utilized in research leading to development of a soon-to-be-tested improved cholera vaccine, Dr. Finkelstein said. A form of the experimental "toxoid" vaccine is being tested at UTSMS and elsewhere and it looks "extremely promising," the Dallas scientist said.

"We've been able to show that immunization with a toxoid prepared from the toxin protects laboratory animals against challenge either with the toxin or the cholera organisms themselves," he said.

Dr. Finkelstein, associate professor of microbiology at UTSMS, explained that the toxoid is a chemically inactivated form of the toxin, treated so that it can no longer cause cholera--"but there's enough material left to stimulate formation of anti-bodies against the toxin and consequently protection against the disease."

Scientists have high hopes the new material will provide longer-lasting immunity, as is now possible with diphtheria and tetanus, and more complete protection against the cholera infection than is afforded by the existing vaccine. The old vaccine, containing killed bacteria, has been essentially unchanged since its development in 1898, Dr. Finkelstein said. It immunizes less than 50 per cent of its recipients, and the protective effect lasts only three or four months.

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Preliminary tests of the new toxoid vaccine, being produced by Wyeth Laboratory under contract with the National Institutes of Health, are scheduled on human volunteers, tentatively to be followed by a massive trial in Asia. Part of the early testing will be done at The University of Texas Medical Branch in Galveston.

"If the vaccine is found to be safe and produce a satisfactory immunologic response," the Dallas scientist said, "it will be tested in Dacca, East Pakistan, beginning next spring in a controlled field study involving approximately 200,000 people," he said. Dr. Finkelstein recently returned from conferences with cholera researchers in Tokyo, Dacca and Bangkok, Thailand.

Pakistan, along with India, annually are swept by cholera epidemics. As recently as 1964, an estimated 100,000 cases occurred in Pakistan, resulting in 30,000 deaths.

The scientific sleuthing that yielded the purified cholera toxin was a long and tedious task for Dr. Finkelstein and his associate, Dr. Joseph LoSpalluto of the UTSMS biochemistry faculty.

Utilizing a complex array of centrifuges, fermenting cylinders, filters and the like, the team sorted through a seemingly endless variety of unimportant proteins, lipids, enzymes and other byproducts manufactured by the lethal cholera bacteria as it grew in a nutritious liquid medium.

Separating the material through filters of varying sizes in a seven-step purification process, the scientists finally emerged with a small quantity of submicroscopic particles of cholera toxin.

"From 10 liters of original material, we ended up with less than 100 milligrams, or a tenth of a gram, of pure cholera toxin," said Dr. Finkelstein. "But that's enough to give cholera to 200,000 rabbits--or probably 1,000 or more people."

Because each byproduct of the separating process was contained in look-alike colorless solutions, hundreds of needle-in-a-haystack tests were required to locate the guilty proteins, detected by their ability to react visibly with their specific antibodies.

Some 650 liters (about 170 gallons) of toxin have been produced so far in the Dallas lab. Samples have been sent to scientists in Thailand, Japan, Australia, Sweden, England and other countries, as well as to a half dozen U.S. research centers.

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In a separate research project, microbiologists Drs. Udom Lexomboon and Finkelstein, working with Dr. Andres Goth, professor and chairman of pharmacology at UTSMS, are testing a series of drugs for their effectiveness in mice against the inflammatory cholera toxin.

No known drug exists that will actually reverse the disease process, Dr. Finkelstein says. That process, in fact, is not yet fully understood.

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The tragic irony of cholera today is that it is a curable disease--yet thousands still die from it, Dr. Finkelstein said.

"Cholera particularly affects people in developing areas--people who are malnourished and have poor sanitation and whose governments are not well developed, so that it's very difficult for backward countries to adequately treat cholera patients," he said.

Recent strides in treatment have dramatically improved odds for survival, Dr. Finkelstein noted.

Basic treatment involves physically replacing lost body fluids and salts, with antibiotics administered to reduce overall severity of the disease. New portable kits containing life-saving fluids, chemicals, and needles and other paraphernalia are making treatment relatively easy even under the most primitive conditions, he said.

While cholera represents an entire spectrum of diarrheal disease, the term mostly is applied to a severe, often fatal fulminating form of infectious diarrhea. Culprit in the malady is a tiny, wiggling, comma-shaped microbe called "Vibrio cholerae." The vibrio exists in several strains, with a particular type known as El Tor blamed for the current worldwide cholera siege.

The El Tor bacteria thrive in the small bowel, multiply furiously and provoke the intestines into a voluminous diarrhea--often at the rate of five gallons per day--which if unchecked can bring death from dehydration and exhaustion in a short time.

The disease is spread through contamination of drinking water or food by the bacteria-laden faces of its victims, often reaching epidemic proportions in a matter of days, Dr. Finkelstein said.

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Thus cholera is not an epidemic threat in the United States or other developed countries with purified water and sewage disposal facilities. But individual travelers can contract the disease, and should be vaccinated before going to afflicted areas.

While no cholera cases have been reported in the U.S. since 1911, the disease had affected this country during earlier pandemics, or worldwide epidemics, in the 1800s "with devastating effects," Dr. Finkelstein said.

The current cholera pandemic began in 1961 and has migrated across Asia to Africa. According to the Center for Disease Control in Atlanta, it is occurring or is suspected widely throughout Southeast and South Asia, the Middle East and northwest Africa.

Widespread jet travel between Asian countries probably has facilitated spread of cholera. The CDC lists Indonesia, the Philippines, Vietnam, Burma, India, Nepal, East Pakistan and Russia--where five coastal cities along the Caspian and Black seas have been closed to tourists--as reporting cases of cholera.

The U.S. government recently shipped 30,000 bottles and 27 drums of the existing cholera vaccine to the Middle East and Europe for use in protecting against the disease, the newspaper "U.S. Medicine" reported last month. It said some of the supply will be stockpiled at U.S. military installations for protection of American servicemen.

A major difficulty in treating cholera is that the disease-producing organism never actually enters the body, Dr. Finkelstein pointed out.

"The cholera vibrios live and multiply only in the intestinal tract--a tube outside the body's tissues. There they liberate their toxin, which probably affects only the nearby cells of the intestinal wall," he said.

If the bacteria were in the bloodstream, they would be much more easily attacked by drugs or vaccines, he noted.

Even if a new vaccine is perfected, eradication of cholera will remain difficult, Dr. Finkelstein says.

"To be effective," he said, "the vaccine would have to be much more widely administered than is possible today. To do this means enormous problems involving expense, personnel and education in economically and culturally backward areas must be overcome."

fourth add cholera

The most obvious and most effective means of control of cholera is improvement of sanitation--"so that people are not obliged to drink contaminated water and eat contaminated food," he observed.

He said a fringe benefit of intensified current research will be an improved understanding of the whole family of diarrheal diseases, of which cholera is only part--diseases "which account for a substantial portion of the mortality and morbidity that people experience, particularly in developing areas."

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