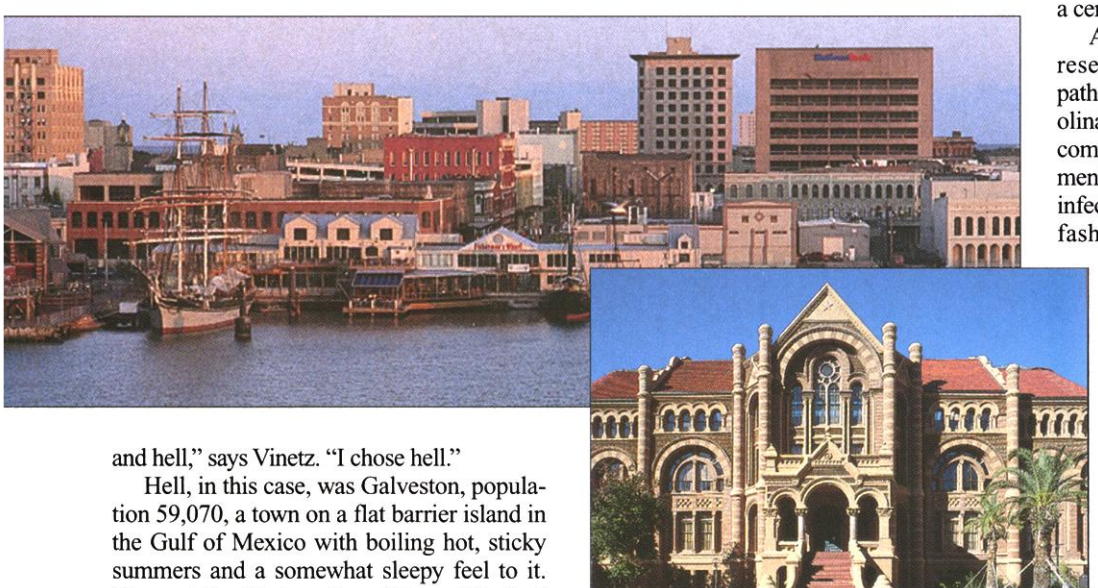
PROFILE

Working in the Hot Zone: Galveston's Microbe Hunters

From a little-known school in a quiet Texas backwater, a world-class center for the study of infectious diseases is emerging

GALVESTON, TEXAS—When malaria researcher Joseph Vinetz finished his postdoc at Johns Hopkins University 2 years ago, he had job offers from prominent universities in exciting cities on the East and West coasts—as well as one from a relatively unknown medical center in a small town in southeast Texas. "It felt like a choice between heaven and hell," says Vinetz. "I chose hell."



Old-world charm. Galveston's past as a "Manhattan on the Gulf" is reflected in its historic waterfront and UTMB's first building, known as "Old Red" (*inset*).

Hell, in this case, was Galveston, population 59,070, a town on a flat barrier island in the Gulf of Mexico with boiling hot, sticky summers and a somewhat sleepy feel to it. Here, at the University of Texas Medical Branch (UTMB), a cadre of virologists and microbiologists is quietly building a topflight center for the study of emerging tropical and infectious diseases, and luring experts like Vinetz, who previously might have scoffed at the idea. The number of faculty members working in infectious diseases has roughly tripled to over 70 during the last decade; funding from the National Institute of Allergy and Infectious Diseases has shot up from $4.4 million in 1995 to almost $10 million this year.

The newcomers are drawn to three departments—pathology, microbiology and immunology, and internal medicine—working together in a Center for Tropical Diseases, which has excellent facilities and a critical mass of bright minds to collaborate with. And they study everything from malaria, hantaviruses, dengue, yellow fever, and hemorrhagic fevers to *Salmonella* and hepatitis. "Every place has its good and bad times," says Alan Barrett, a virologist who moved here from the University of Surrey in the United Kingdom 7 years ago, taking his research group of five with him: "This is our heyday. People want to come and work here."

In an example that astonished many in the field, Galveston now seems set to recruit C. J. Peters, a top virologist from the Centers for Disease Control and Prevention (CDC) in Atlanta. Although he hasn't signed a contract yet, Peters says he's "99% decided" that he'll go. "Good people always attract good people," comments virologist Charles Calisher of Colorado State University in Fort Collins. "It's like a black hole!" "It's a fantastic group. They may well become *the* center for tropical medicine in the world," adds Ian Lipkin, a molecular biologist at the University of California, Irvine, and one of the discoverers of the West Nile virus strain that surfaced in New York City last summer.

UTMB is also planning to build a biosafety level 4 (BSL-4) lab—the type in which spacesuit-clad researchers work under the most stringent containment conditions—of which there are currently just a handful in the world. That would allow Galveston researchers to study any virus they want to and really put their center on the map, say colleagues.

Back to the future

If all that seems ambitious for such a small town, UTMB researchers like to point to Galveston's past. Once Texas's main seaport—during the 19th century, the island ranked as a Manhattan on the Gulf—Galveston was frequently plagued by scourges like yellow fever, cholera, typhoid, and dengue. Turning a vulnerability into a strength, the University of Texas opened its first medical school here in 1891; in its early years, it was one of the nation's finest. But in the 20th century, as the city itself slipped from prominence, the school lost its edge. A monstrous hurricane killed over 6000 Galvestonians in 1900 and flattened a large swath of the city, setting off a century of economic decline.

As a result, UTMB didn't have a strong research tradition when David Walker, a pathologist from the University of North Carolina, Chapel Hill, seized the chance to become the new head of its pathology department in 1987. Walker had been fascinated by infectious diseases long before they became fashionable and was determined to make them the mainstay of his department. His own research interest was how intracellular bacteria such as *Rickettsia* and *Ehrlichia* cause disease, but he wanted UTMB to study other bacteria, viruses, and parasites as well, especially those occurring in Latin America. "I thought in Galveston we had to look south," he says.

The university supported Walker with money to gut a charming but rundown 1920s building on campus and turn it into a state-of-the-art lab with biosafety level 3 rooms, which was completed in 1995. But declining revenues in health care in recent years have tightened budgets at UTMB, as in many other academic health centers, and "we're just as pinched as any other department," he says. Much of the growth had to come from outside funding. In addition, Walker says he strategically hoarded some $6 million between 1990 and 1995, when the university could still spend in style, then used it after the lab renovation to do what some colleagues say he does best: snatching up talent.

Perhaps Walker's biggest coup came in 1995, when he hired Robert Shope and Robert Tesh, two world-renowned experts in arthropod-borne viruses, or arboviruses, from Yale University. Like many other places, Yale at the time was shifting focus to the AIDS pandemic, while more obscure viruses were falling from grace. And the lab came under heavy fire after a visiting French scientist became infected with the Sabia virus, an inci-

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dent an investigation blamed on lapses in safety procedures. "Yale wasn't very supportive, and they would never invest in infrastructure," says Tesh. "I decided I had to get out before I got too old to move."

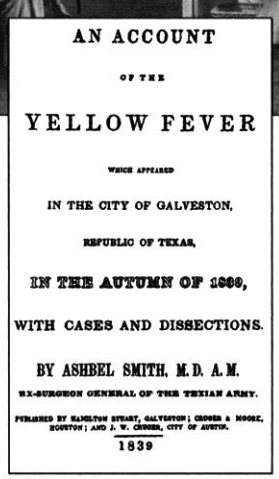
Galveston seemed like an up-and-coming place, he says, and the facilities were great. Besides, he knew Barrett, and one of Tesh's postdocs, Scott Weaver, had just decided to move from the University of California, San Diego, to Galveston. And Galveston was just a short flight from Latin America, where he had many collaborators and did most of his fieldwork.

Shope, 66 at the time, had led Yale's Arbovirus Research Unit for 24 years and earned himself a reputation as a senior statesman of virology; together with Nobelist Joshua Lederberg he had authored *Emerging Infections: Microbial Threats to Health in the United States,* a 1992 Institute of Medicine report that served as a wake-up call to the country. Few thought at his age he would leave New England for a new adventure in Texas. But once Tesh decided to leave, the choice was easy, says Shope, especially since the duo had built up the World Reference Center for Arboviruses together, a frozen treasure of thousands of virus strains and related reagents, funded by the National Institutes of Health. "It didn't seem feasible to have half of it at Yale and half of it in Galveston," says Shope. So he retired and followed Tesh south, taking the collection along.

Shope spends most of his time working with the collection and serving as a "walking encyclopedia" of virology, say colleagues. Researchers around the world use the collection to identify an unknown virus or characterize a particular viral strain. Tesh spends much of his time in the field in South America, studying the growing army of deadly agents there, such as yellow fever and arenaviruses, which cause hemorrhagic fevers. To better understand what causes new outbreaks, Tesh also plans to study how the ecology of a virus changes when the rainforest is cleared to make room for people. *Leishmania*, the parasite that causes leishmaniasis, once was mostly limited to forested areas, but now infects dogs and horses and has become an urban disease; the question is whether viruses are doing the same, says Tesh.

With "the two Bobs," as Shope and Tesh are fondly known, Galveston's lure rose exponentially. Vinetz, for instance, says the presence of a strong arbovirology group was one of the factors that persuaded him to come. Galveston's collective knowledge about mosquitoes and other insect vectors is a big plus, he notes. And it pays off: Last year, Vinetz found the gene encoding the mosquito gut protein that *Plasmodium*, the malaria parasite, uses to break through the insect's gut wall and travel to its salivary glands. Tesh also urged Charles Fulhorst, a virologist who was on Yale's payroll but had been stationed at the CDC for several years, to join him and Shope in Galveston. Fulhorst is one of the researchers who's eagerly awaiting the BSL-4 lab; at CDC, he practically lived in one, he says, and he's eager to do more work on some hantaviruses and arenaviruses. (The Sealy & Smith Foundation, which exclusively supports UTMB, has pledged to pick up the tab for Galveston's BSL-4 lab.)

The promise of the new facility is also one of the things drawing CDC's Peters. A virus hunter with 3 decades of experience—he was immortalized in books like *The Hot Zone* and flicks like *Outbreak*—Peters currently directs CDC's Special Pathogens Branch. But there the emphasis is always on responding to outbreaks, he says; at an academic center like UTMB, Peters thinks he'll have the time to dig into more basic virological questions. For instance, he'd like to study the molecular mechanisms by which hemorrhagic fevers cause disease and death. "For my personal scientific fulfillment, I'd like to get to the bottom of some of these problems," says Peters. "At CDC, that's not really our mission. … We don't have the funding, people, space, etc., to do that."


AN ACCOUNT

OF THE

YELLOW FEVER

WHICH APPEARED

IN THE CITY OF GALVESTON,

REPUBLIC OF TEXAS,

IN THE AUTUMN OF 1839,

WITH CASES AND DISSECTIONS.

BY ASHBEL SMITH, M.D. A.M.

EX-SURGEON GENERAL OF THE TEXIAN ARMY.

PUBLISHED BY HAMILTON STUART, GALVESTON; CROCKER & MOORE, HOUSTON; AND J. W. CRUGER, CITY OF AUSTIN.

1839

Battling infections. UTMB, established in 1891 to combat tropical diseases that plagued Galveston, has recently become a leading center for research on the organisms that cause them.

CREDIT: (TOP) BLOCKER HISTORY OF MEDICINE COLLECTIONS/MOODY MEDICAL LIBRARY

A different culture

One of UTMB's big attractions, says Vinetz—and, in fact, it's repeated by almost everybody else on campus—is that researchers here seem to collaborate more easily than elsewhere. Perhaps it's because there just happen to be few prima donnas among senior researchers, some say. "Usually, big egos get in the way of research," says Barrett. "It's very strange, but here everybody wants to work together." Others say it's a Galveston thing, a unique local culture—call it an island state of mind. "It's a low-traffic, no-stress place, and it's very congenial," says Vinetz. But whatever the cause, "it's an extraordinary scientific environment that you could find nowhere else in the world."

One example is a daring project in which UTMB virologists and pathologists have joined forces with the university's structural biologists—who probe the three-dimensional structure of proteins—to develop new defenses against the threat of bioterrorism. Led by Shope and David Gorenstein, who heads UTMB's Center for Structural Biology, the team first identified three virus groups that terrorists are likely to employ: flaviviruses (which include dengue, yellow fever, and the West Nile virus), alphaviruses (responsible for several types of brain infections), and the arenaviruses. Now, they are using combinatorial chemistry to find small molecules to thwart some key viral proteins in each group. The collaboration, funded by a $3.7 million grant from the Defense Advanced Research Projects Agency, is "a unique opportunity," says Gorenstein: "In academics, you don't often work on the big picture."

Not that there aren't any drawbacks to working in Galveston. One problem, some say, is that UTMB doesn't have the stellar reputation of some of the universities that it draws its people from. In her previous job, says immunologist Lynn Soong, who studies leishmaniasis, if she needed reagents or knockout mice, she just had to say she worked with Dr. So-and-so at Yale, and colleagues from other institutions would send them along. Mentioning she's from UTMB doesn't do the job as quickly, she has found: "For some people, it's the first time they

hear about this university."

Another frequent gripe—besides the unforgiving climate—is that Galveston is, well, a small town in Texas. For Vinetz, it didn't turn out to be the hell he expected; but senior researchers do concede that some people from the East and West coasts absolutely refuse to live here. "In job interviews, I always try to be up-front about it. This is not the center of the cosmos, and there's not a lot to do," says Barrett. "You can work, you can work, or you can get in your car and drive to Houston." But most newly arrived Galvestonians, including UTMB president John Stobo, say they have no regrets about moving here; they like to point out the city's good points, such as considerable historic charm and affordable housing. Stobo, a Massachusetts native and a former vice dean of Johns Hopkins University School of Medicine, has even taken to wearing cowboy boots, which he enjoys showing off. "Once they settle in, most people come to like Galveston," he assures.

And Galveston is trying to keep them coming. UTMB acknowledges that several parts of its infectious diseases profile could be beefed up; for instance some "card-carrying epidemiologists" would be very welcome, says Stanley Lemon, who came here in 1997 to head the department of microbiology and immunology. Lemon studies the molecular biology of hepatitis C, but says he would also like to answer basic epidemiological questions, such as why it infects more Mexican Americans than Caucasians. UTMB is also interested in stepping up surveillance for emerging infections along the Mexican border, says Lemon. Last year, there was a large outbreak of dengue in Texas, and a girl died—the first U.S. casualty from the disease in over 3 decades. "That's a signal of what we can expect," says Lemon. Walker adds that the group also would like to strengthen its efforts in vaccine development and bioinformatics.

With new deadly pathogens popping up almost every year, there's certainly no dearth of study material. And new molecular techniques have made it possible to study and fight them right down to the molecular level, says Walker. "That was my dream, that was what I was hoping would happen," he adds. "It's sort of fun to see so many people involved in doing it." **–MARTIN ENSERINK**

NATIONAL SCIENCE FOUNDATION

Information Technology Takes a Different Tack

Challenged by a White House committee to change its ways, the National Science Foundation is looking for far-out ideas in computer science

"Excellent," raved one reviewer about a preproposal from James Allen, a computer scientist at the University of Rochester in New York. But Allen says another dismissed it as "impossible."

Normally, such wildly conflicting reactions would doom a grant application submitted to the National Science Foundation (NSF). But not this time. In fact, the skepticism may have helped: An NSF official, intrigued by the wide variation, plucked Allen's preproposal from the discard pile and gave him the green light to seek up to $3 million over 3 years as part of the agency's new information technology (IT) program.

NSF isn't breaking out of its shell on a whim. By taking more risks than usual, officials hope to encourage researchers to submit proposals that are likely to be more innovative than those the agency traditionally supports. Here's how program manager Michael Lesk describes what he's looking for: "If somebody not in your research group but familiar with your published papers could predict your proposal, perhaps you should rethink it."

As lead agency for a 5-year, $5 billion federal IT program, NSF hopes its boldness will rub off on the other players. And some researchers think that such a fresh, frisky approach would work well in NSF's other programs, ranging from exploring the early universe to plumbing the ocean depths. "The IT program is heading in the right direction," says computer scientist Jonathan Smith of the University of Pennsylvania, Philadelphia. "The question is how fast an agency that is very set in its ways can morph."

NSF officials are not averse to morphing, but they say it is up to each discipline to decide whether to adopt the more freewheeling approach being followed by IT program managers. If the reaction to the IT program is any guide, the community is ready: Computer scientists submitted more than 2000 proposals for the $90 million program, making it one of the largest competitions ever run by NSF's Directorate for Computer and Information Science and Engineering (CISE). Allen's idea—an interdisciplinary research center to study the mechanics of human speech and to create computers that can carry on conversations—was one of 200 that made the first cut; he'll know this summer whether it will be funded. "It's energized the community," says CISE director Ruzena Bajcsy. "Anybody who is anybody in the discipline has applied."

The program's shakedown cruise hasn't been trouble-free, however. NSF officials fret that they are seeing too few innovative ideas from researchers, who perhaps haven't heard—or don't believe in—the IT program's new tune. They've also scrambled to recruit reviewers, as so many computer scientists are already involved in the competition. Researchers, on the other hand, worry that the program's low—less than 10%—overall success rate will scare away entrants next year. To increase the number of future winners, they are pushing Congress to double the program's budget in 2001, despite skepticism from some lawmakers.

BEATING THE ODDS

Category	Budget (in millions)	No. of preproposals	No. of finalists	No. of awards
Large grants ($500,000 to $3 million/year)	$63	943	200	~30
Small grants (Under $500,000/year)	$27	not sought	1156	~130

Crowded field. High interest will mean a low success rate for NSF's IT program.

SOURCE: NSF

Overcoming doubts

Whether or not Congress agrees, researchers say NSF deserves credit for grasping an opportunity to do things differently. That opening was created by the President's Information Technology Advisory Committee (PITAC), a high-profile panel packed with computer company CEOs and prominent academics. Last year, it issued a report aimed at recreating the federal funding climate of the 1970s and 1980s that produced the Internet and other computing revolu-