

Much Too Tired

Mr. Post's escalating fever after a monthlong trip into the bush was not a good sign

CHRISTOPHER POST WAS NOT YET HOME WHEN HE NOTICED THE crimson spot, roughly nickel-sized, on his left biceps. Returning from the trip of a lifetime, a monthlong safari in Africa, he was tired, achy, and hot. Maybe it's eczema, the 50-year-old stockbroker reasoned. He'd be better in a couple of days.

But a few days later, Mr. Post was worse, with a higher fever. The spot on his arm was bigger. His internist was out of town, so he drove to a nearby hospital.

"Did you use malaria pills in Africa?" asked the emergency-room physician.

"Yes, and I also got shots before leaving," Mr. Post said. For the trek to Tanzania and Rwanda, he had prepared by the book: yellow fever and typhoid vac-

cines, a quinine-type drug to stave off malaria, and a stash of diarrhea pills.

"I'm not sure about that bug bite," the doctor mused, "but your fever is straight from the textbooks. Sounds like malaria to me. We'll start with a blood exam."

An hour later, he returned with microscope slides.

"Mr. Post," he said, looking grave, "your problem is not what I thought. Here are your blood smears. Our hospital is not prepared to take care of you. They're expecting you at the university hospital as soon as you can get there."

Andy Peters was the internal medicine resident on duty at the university hospital ER that day. He liked figuring out infectious diseases—the more exotic, the better. Andy's jaw fell as he scanned through Mr. Post's blood smears. He had expected to see the delicate rings of the malaria parasite within red blood cells. Instead he saw wavy, whip-tailed creatures swimming free like eels. By microscopic standards, they were big eels—twice as long as the patient's blood cells.

Andy consulted descriptions of another blood-borne parasite from Africa: *Trypanosoma brucei*. Bingo. Perfect match.

He headed to the patient's room, introduced himself, and explained his discovery: sleeping sickness.

That's when Christopher Post decided to make out his will.

Swift death is common among victims of East African trypanosomiasis, the variety infecting Mr. Post. In 1906, it killed at least half of Uganda's 6 million inhabitants. West African, or Gambian, trypanosomiasis is the more insidious, classic sleeping sickness, causing creeping inflammation of the brain that over a period from months to years gives rise to seizures, psychosis, stupor, coma, and death.

But whatever its geographic subtype, the insect vector of African →



Trypanosomiasis infects an estimated 300,000 Africans. In some villages, half of the residents may be infected. And in the Democratic Republic of the Congo, the disease is thought to cause as many deaths as AIDS. Because of the parasite, vast regions of Africa are unsettled.

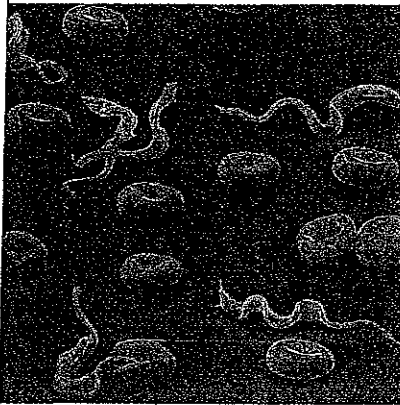
VITAL SIGNS

→ trypanosomiasis is always the same: the tsetse fly. Twice as big as a housefly, with predatory mouth parts and scissorlike wings, it breeds in dark, moist niches of sub-Saharan forests and thickets. East African tsetse flies acquire trypanosomes from the blood of infected animals, typically savanna-dwelling bushbucks, or infected humans. West African tsetses tend to acquire the parasite by feeding off infected humans. In both locales, parasites multiply in the fly's stomach, then migrate to salivary glands. At that point, one bite is all it takes to launch a new infection in another animal or human.

Weeks into his illness, Mr. Post recalled brushing off some "really big insects" in Africa. However, at the time, he had no idea they were tsetse flies. Nor in his wildest savanna dreams could he have imagined the battles these parasites would wage in his body.

Trypanosomes have a canny way of dealing with the body's immune de-

fenses. As early as 1910, researchers noticed wave after wave of parasites in the blood of sleeping sickness victims. Today we know that each wave represents a new generation with altered surface proteins. This new coat triggers a fresh volley of host antibodies. The antibodies work at first, but ultimately they fail in



Trypanosoma brucei, the parasite that causes sleeping sickness, is about twice as long as a red blood cell.

the face of yet another battalion of re-configured parasites.

By the time Mr. Post reached the university hospital, the battle in his bloodstream had been under way for weeks. Not only had the parasites glutted his bloodstream, but he also was taking friendly fire from his own immune system. He had severe anemia, a dangerously low platelet count, malfunctioning kidneys, and a baggy, inflamed heart, all due to his own antibodies attacking his own tissues.

The most dreaded complication of sleeping sickness is brain infection. A test of Mr. Post's spinal fluid would show if the parasites had infiltrated his central nervous system. If we found them there, our only hope for ridding Mr. Post of the infection was melarsoprol, an arsenic-based parasite poison that also kills about six percent of patients.

We have very few treatment options for sleeping sickness, and all of them are toxic. To pick the right drug, we

OLIVER MECKES/PHOTO RESEARCHERS



THE DAYTIME NON-DROWSY CONGESTED STUFFY HEAD SORE THROAT COUGHING

must identify the particular strain of the parasite and its stage of infection. Needless to say, when I got called about Mr. Post, I was concerned. I am the local tropical medicine expert, but I'm not above asking for help.

My first call went to the Centers for Disease Control in Atlanta. They operate a 24-hour hotline for crises involving parasites like *Trypanosoma brucei*. After hearing that Mr. Post's spinal fluid was clean, the doctor on call recommended suramin, another toxic remedy, used since the 1920s. The only problem was that the CDC has the only supply of suramin in the United States. That meant it could not reach Mr. Post until at least the following day.

Could we afford to wait? Over the past 12 hours, his fever had shot even higher, and his follow-up blood smears showed wall-to-wall parasites. In desperation, we gambled on pentamidine, an antiparasitic drug we had in the hospital pharmacy. The following afternoon we started suramin.

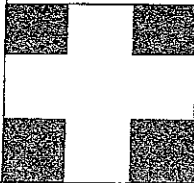
The next few days were rocky. Within hours of treatment, the drugs killed the parasites, spilling their remains into the bloodstream. That put the immune system into overdrive. Mr. Post's blood count plummeted, his heart and kidneys worsened, and most telling of all, the bite on his arm grew huge, its borders jagged and magenta. Our dermatologist hadn't seen anything like it.

But two weeks later, the victim was the victor. Just about everything we take for granted in modern health care—technology, teamwork, and drugs—contributed to beating the infection.

Today, Mr. Post and I have a special bond. After all, I'm not likely to see another case like his soon. Prior to his arrival at the emergency room, only a handful of red-hot sleeping sickness infections had been seen in the United States in a decade. Mr. Post, in turn, gained a perspective on tropical medicine no textbook could ever teach. Compared with that of fellow sufferers, Mr. Post's care was a high-tech luxury and a miracle beyond imagination.

In the land of the tsetse fly, where even the most fundamental health care is scarce, thousands die from sleeping sickness every year. ☒

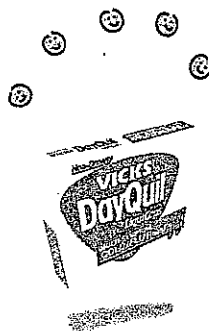
THE DOCTOR IS IN



Almost 30 years ago, Claire Panostan Dunavan was a medical volunteer in Haiti, where she worked in a hospital without electricity or telephones. "I've been hooked on tropical medicine and international health ever since," she says. Dunavan is a clinical professor of medicine and infectious diseases at the UCLA School of Medicine.

THE CASE DESCRIBED IN VITAL SIGNS IS BASED ON A TRUE STORY. SOME DETAILS HAVE BEEN CHANGED TO PROTECT THE PATIENT'S PRIVACY.

Also try the lower decibel way to
feel alert when you have a cold.



ACHING FEVER SO YOU CAN GET BACK YOUR DAY IN A MINUTE FROM THE MAKERS OF DAYQUIL

Vital Signs

A fearsome infection spoils a honeymoon

By Claire Panosian Dunavan

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Dengue fever

The message was brief but urgent: "Honeymooner arriving tonight from Tahiti. Has fever, headache, hemorrhagic rash. Will take ambulance to our emergency room. Can you meet her there?"

That year, I took care of three returning newlyweds with the same tropical woe—but none as sick as Susie Gold.

Susie and her fiancé, Jeff, had resolved to have a one-of-a-kind wedding in the South Pacific, where they would exchange vows under a cabana of palm fronds. Everything went off without a hitch, but five days later Susie developed teeth-chattering chills. Her muscles felt sore and bruised. At first she downplayed her symptoms, figuring she was wiped out from the wedding or fighting a bug she had picked up on the plane. It would pass.

Sure enough, a day later, she was better. She and Jeff resumed snorkeling and strolling along the beach, their happiness marred only by sunburned noses and mosquito bites.

The next morning Susie's head and eyeballs ached furiously, her brow was hot, and her legs sported a rash that looked like purple shooting stars. Her biggest scare came after flossing her teeth. She tasted salt, looked in the mirror, and saw bright red blood.

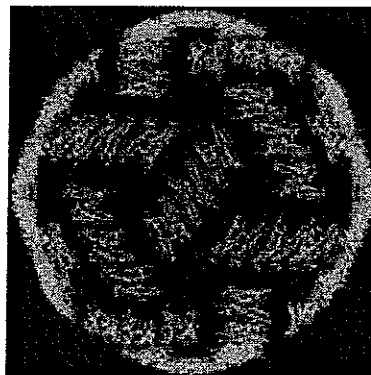
Jeff called Susie's dad, a psychiatrist. He listened to Susie's symptoms, then rang off to consult with the family internist. Thirty minutes later he was back on the line.

"Jeff, you've got to bring Susie back. Don't worry; I've arranged everything. Once you land in Los Angeles, an ambulance will take her straight to the university hospital."

If Dr. Gold had actually spoken to me before Susie boarded her plane, I probably would have vetoed the daylong wait before she was seen by a doctor. To an infectious-diseases specialist, her constellation of fever, headache, and pinpoint bleeding in the skin indicates meningococcemia until proven otherwise. Meningococci are bacteria that invade the blood and the meninges that line the brain. A 12-hour delay in receiving antibiotics can be the difference between life and death.

But deep in my gut, I worried that Susie might have another misery that can mimic meningococcemia. Starting in the 1980s, dengue—a mosquito-borne virus that dogged Allied and Japanese troops during World War II—made a stunning comeback in the Pacific, Southeast Asia, and the Caribbean. Like meningococcal infection, dengue also causes fever, headache, and hemorrhagic rash.

A small, black-and-white mosquito, *Aedes aegypti*, is dengue's main vector. It loves to breed in water-filled crockery, cisterns, trash containers, and spare tires that surround human habitation in the tropics. That's a lucky coincidence for an insect whose survival depends upon blood meals. In turn, the blood-borne dengue virus profits from its vector's feeding habits. With the slightest provocation, the female *Aedes* stops her blood meal, only moments later to resume probing and siphoning the same or another nearby victim. Thus, a lone mosquito carrying dengue from a previous host can spread the virus to multiple recipients.



A protein shell surrounds and protects

After an *Aedes* loaded with dengue inoculates its victim, illness begins within seven days. Although symptoms range widely, fever, chills, and headache often herald the attack, along with facial flushing, swollen glands, and a mild sore throat. Then comes a deceptive lull before dengue's encore fever arrives. This later stage features an array of skin rashes as well as dengue's famous aches, otherwise known as breakbone fever.

the genetic material of the dengue virus. Researchers recently determined the shell's structure.
Image courtesy of Michael G. Rossmann/Richard Kuhn/Purdue University

Dengue's most dreaded complications are hemorrhage and shock, which typically strike children and adolescents battling the infection for a second time. During a second bout of dengue, old antibodies are thought to bind to the new virus, but they fail to clear it because of changes in the new infecting virus. Instead, antibody-virus complexes are engulfed by watchdog cells called macrophages. During severe infections, macrophages can release chemical signals that cause capillaries to leak, which results in bleeding and, at times, drastic depletion of plasma volume.

Still, Susie's case didn't stack up perfectly for dengue because her bleeding didn't fit with a first-time infection. A true diagnosis would be tricky: There's no easy test for dengue.

Eight hours later I got a call on my pager from our emergency room. Susie had arrived.

I hurried to the cubicle where she lay pale and sweaty but lucid. Her blood pressure was low and her pulse was high. She had bleeding gums and a sprinkling of hemorrhagic dots on all four extremities, just as she had described. Otherwise, the physical exam revealed only a few lentil-size lymph nodes and a tender liver edge below the right rib cage.

"She didn't eat a thing on the plane," Jeff said, his voice tinged with worry, "and when she stood up at the end of the flight, she nearly fainted."

Drip, drip, drip: An intravenous set was running saline into Susie's vein at the fastest rate the tubing would allow. Adding fluid would help bring up her blood pressure and prevent her from going into shock.

"Her vascular volume is low," I replied, avoiding the term "shocky," which the ER resident had used to describe the washed-out bride. "Right now she needs lots of fluid. We'll deal with food later."

I turned to Susie. "Don't worry. It will be rough, but you'll pull through."

At that point I left to review lab tests. Just as expected in a major viral assault, Susie's leukocytes and platelets were low. That meant she was depleted of cells that counter infection and bleeding. At the same time, her liver enzymes were elevated three- to fourfold, corresponding to the swollen, tender edge I felt on exam. Everything fit with dengue, yet nothing was truly diagnostic. Meanwhile, it would take 48 hours before blood cultures were known to be negative for meningococcus.

Sometimes being a purist is a mistake in medicine. Although I was confident that Susie had dengue, a disease for which antibiotics are ineffective, I asked myself: In her shoes, would I want antibiotic treatment until a serious bacterial infection was 100 percent excluded? My answer was yes.

"Let's start ampicillin and ceftriaxone for now," I said to the resident, "but don't forget to order an antibody test for dengue fever. It may take a long time to get the result, but it could be our only proof."

My next stop was the library. All day a vague memory had nagged me. Hadn't I seen a case report describing hemorrhage and shock in first-time dengue? Or was my mind playing tricks on me?

The American Journal of Tropical Medicine and Hygiene came through: "Dengue shock syndrome in an American traveler with primary dengue 3 infection" (March 1987). In the 15 years since that report, with the blossoming of dengue and exotic overseas travel, such cases in tourists are no longer rare. For reasons that are unclear, even these first-time infections can occasionally lead to bleeding and shock.

As for Susie, she spent the next few days in the hospital while her plasma volume restored, her bleeding stopped, her skin hemorrhages cleared, and her lab tests normalized. As expected, her blood cultures remained negative, so we finally shut off her antibiotics 48 hours after admission. Three days later, when she and Jeff were ready to return to the East Coast, the only remnant of her ordeal was depression. Post-dengue blahs, sometimes referred to as neurasthenia, were well known to British colonials. I reassured Susie that her mood was normal and would gradually improve on its own. The following week her dengue antibody sent from the emergency room finally came back positive.

Web Resources:

For an overview of diverticulitis, see <http://merck.praxis.md/bpm/bpmviewall.asp?page=CPM02GA363>.