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This illustration, circa 1700, showing an animal-to-human blood transfusion, attests to the desire to replace the essential fluid.

SLICKER BLOOD

A REMARKABLE LUBE JOB | BY DOTTIE HORN

An ambulance, sirens piercing, speeds to help a stabbed man in hemorrhagic shock. He has lost so much blood that his heart isn't getting the oxygen it needs to beat properly. His blood pressure drops. The flow of blood through the smallest vessels, where the nourishment of tissues and exchange of gases take place, falls to near zero. Tissues begin to die.

The ambulance arrives, but ambulances don't carry blood, which the man desperately needs. The emergency technicians infuse saline into his veins in an attempt to restore the volume of his blood to normal. Saline does not stay within arteries and capillaries, but travels through them, requiring that more and more fluid be infused. Even so, saline is the liquid of choice for nonhospital resuscitations. The alternative, a solution containing colloids such as albumin or starch, stays within veins, but can elicit a dangerous allergic reaction.

The ambulance technicians rush into the ER with the hemorrhaging man. Physicians and nurses prepare for a transfusion; it's their turn to take over the struggle to restore the normal flow and pressure of fluid through vessel walls.

Such struggles began almost as soon as the circulatory system was discovered in 1628, believes Marina Kameneva, associate professor of surgery at the School of Medicine. Artworks from the 18th century showing blood transfusions from animals to humans attest to the desire to replace the essential fluid. Today, despite blood banks, physicians face shortages and the impracticality of using stored blood in some emergency situations—so researchers search for a convenient blood substitute. As of now, the Food and Drug Administration has not approved an artificial blood product for use in humans.

Kameneva is not seeking to develop a blood replacement. A PhD in mechanical engineering, she takes a different approach. Since she began studying blood 25 years ago at Moscow State University in her native Russia, she has asked questions about its mechanical properties. Questions such as—What is its viscosity? What are the characteristics of its flow through microscopic vessels? How can we make it flow better?

In an attempt to answer these questions, Kameneva recently induced severe hemorrhagic shock in rats by slowly taking 50 percent of their blood. She then tried to resuscitate the animals. In her control group, she infused the animals with a solution of saline or colloids. Their blood pressure and blood flow through their tissues improved only slightly, and they all died.

In her experimental group, Kameneva infused a new solution—saline mixed with a tiny amount of a substance she has named HemoMax. The results were dramatic. The blood pressure did not reach normal, but the volume of blood being pumped through the heart improved. In fact, blood flow to tissues increased to levels that were higher than before she induced shock. "Not one animal treated with HemoMax died," says Kameneva.

She has a patent pending on HemoMax, which she created by modifying a substance extracted from plants. HemoMax allows blood to flow more easily through vessels, especially through the microscopic capillaries so tiny that red blood cells must alter their shape in order to squeeze through. She is conducting further tests, yet believes the compound could be used to treat not only hemorrhagic shock but also the host of other diseases that affect circulation through tissues, including diabetes.

Kameneva's invention has been dubbed the "STP of blood," which is not so far off. "We make blood slippery," she says. "Blood is flowing faster through small vessels because it's getting this additive."

It makes perfect sense to Kameneva that she would apply her understanding of petroleum engineering to blood. In terms of flow, the hydrodynamics are the same. However, blood is far more complex than petroleum—it is alive, subject to numerous pathological variations, and full of gases, nutrients, and cells. "It's an amazing fluid," Kameneva says. For her, it's more appealing to study than "Texas tea." ■

THE LIFE YOU SAVE MAY BE YOUR OWN

At any given age, a man is more likely to die from a heart attack than a woman of the same age. At age 40, he is six times as likely to die. At age 50, four times as likely and at age 80, he is twice as likely. Marina Kameneva, professor of surgery, asked why.

Kameneva compared the blood of 47 premenopausal women with that of 50 age-matched men. The male blood was more viscous and its red blood cells were less capable of changing shape, less "deformable." Red blood cells, however, need to be supple. They are typically eight microns tall, and must maneuver through capillaries with diameters as small as three microns. The stiffer male cells might never make it.

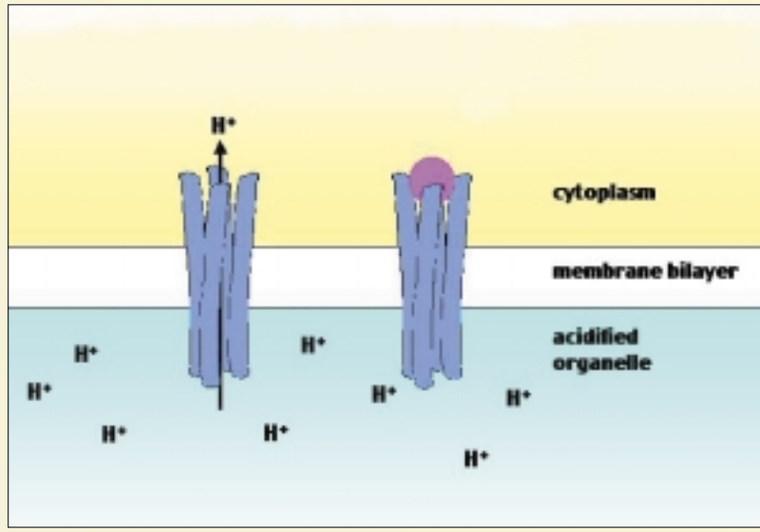
Premenopausal women's blood flows better because it is younger. Menstruating women lose red blood cells every month, and the body replenishes the lost cells with new cells. As a result, premenopausal women's blood has 80 percent more young red blood cells and 85 percent fewer old red blood cells than male blood. The young cells are less dense, which means freer-flowing blood. The young cells also are more flexible, slipping through capillaries more easily.

You don't have to menstruate to rejuvenate your blood; you can simply donate it. One study of middle-aged men found the risk of heart attack 86 percent lower among blood donors. Consider calling the Red Cross today. *—DH*

DRAMATIC ORGANELLES

WEISZ EXPLORES THE GOLGI

BY REBECCA SKLOOT AND ERICA LLOYD



TOP: COURTESY WEISZ ; BOTTOM: KAPELEWSKI/CIDDE

ABOVE: Weisz (middle and seven-months pregnant) with lab crew (from left) Gregory Gibson, Mark Ellis, and Jennifer Bruns. TOP GRAPHIC: Weisz selectively alters the pH of the Golgi apparatus by expressing M2, an influenza protein. M2 channels hydrogen ions from the Golgi's acidic compartment into the neutral cytoplasm, which equalizes the pH. When M2 (shown above in blue) is blocked with certain drugs—e.g., an antiviral compound (purple ball)—it cannot alter pH.

Few people pay attention to the cellular bodies called organelles; even fewer can say there's one they truly love. Ora Weisz is different: She will tell you the Golgi apparatus is her favorite.

Each organelle, like an organ, takes on a specific task—some break down carbohydrates and detoxify drugs, others transport enzymes that keep the cell clean. Among other responsibilities, the Golgi's duty is to receive and ship proteins—it processes the prized freight, then routes it to various locales. Weisz thinks the Golgi looks like a stack of flattened bricks connected end-to-end by a long ribbon. Those "bricks" are really cisternae, a series of continuously changing caverns through which the cell smuggles proteins, later to be released into the cell encased in bubble-like transport vessels created from the Golgi's surface.

Weisz is an assistant professor of medicine and of cell biology and physiology at the School of Medicine. She admits, by the way, that she also is fond of Elvis Presley memorabilia and has taken to collecting it. The stuff is a bit kitschier than organelles, yet she thinks it's still pretty neat. She couldn't tell you exactly what draws her to the King, however. But why she admires the Golgi, the organelle charged with the weighty task of putting a protein—the fiber of life and death and health and disease and growth and aging—where it is supposed to go, well that's clear enough.

How the Golgi accomplishes its tasks is not so clear. "Ten years ago we thought we knew the Golgi," says Weisz. "Yet every few years there's a huge uproar about exactly what's going on in there."

Weisz has spent years studying cellular protein trafficking. These days, she is examining how proteins get around in epithelial cells, which communicate between the body and its external environment. Epithelial cells line body cavities, cover the body as skin, and set up gateways at any surface that interfaces with the world. Because epithelial cells face two distinctly different worlds, they have two distinctly different functions. They line the walls of our intestines, for example, where they absorb nutrients, then transport them to the blood. To accomplish this, the cell surface facing the digestive tract has proteins that import, and the cells on the opposite side export. These cells are polarized—they have different proteins at each pole. If this polarity tips off balance, things can go awry.

For example: "A huge number of cancers affect epithelial cells, and one of the first things that happens is you get a loss of polarity," says Weisz. "So trying to understand what is important in developing and maintaining polarity in normal cells is the obvious first step for understanding it in disease."

Weisz asked the question: *How do these surface proteins know which pole to go to?* One thing the scientific community knows for sure is that the compartment in the Golgi where proteins are sorted for delivery to either pole is the only acidified environment proteins see on their way to the membrane. She tried to alter the Golgi's pH to see what would happen but ran into a problem. The only means for altering organelle pH is through compounds that simultaneously change the pH of all organelles. Weisz couldn't change the Golgi's pH without changing the pH of every organelle.

"You're knocking out all the acidification in a cell and then trying to ask what happens to one small step in the trafficking," she says. Weisz had effectively taken a sledgehammer to the problem.

She was, however, able to come up with a way to use an influenza protein, called M2, to selectively alter pH in certain polarized cells. "The way I was trained," she says, "if you don't have a piece of equipment you need, you make it." Weisz is still refining the M2 method, but has already used it to dispel a popular hypothesis regarding a defect in acidification related to cystic fibrosis.

M2 has refueled Weisz's explorations of that mysterious network of passageways known as the Golgi. "It's just so beautifully organized," she says with a smile. "It's got so many functions and levels of complexity essential for cells, it's quite amazing. More than anything, it's a dramatic organelle. We should know more about it than we do." ■

LATENCY AND TB

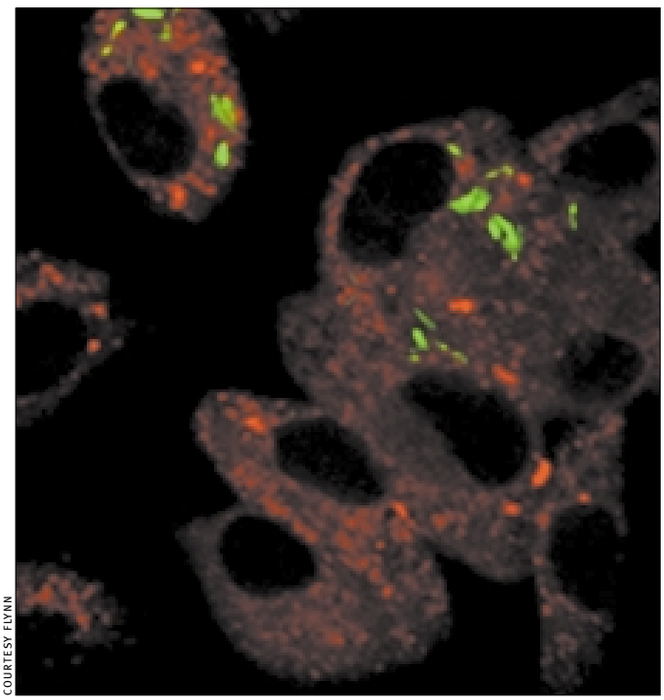
WHAT KEEPS THE DEADLY PATHOGEN AT BAY? | BY ERICA LLOYD

Overheard: Two men on a sidewalk, catching up. One leans in as the other sits on a window ledge and does the talking. He tells the story of how he ended up in not only the same hotel, but the same *room* where the cops raided them that time. Wild. He was living at the shelter, see, then a nurse told him he had to stay alone in the hotel for a few weeks. They thought he had TB. He did. It was kind of crazy, hospital tests—but he's okay now. . . .

One third of the world's population is infected with *Mycobacterium tuberculosis*, the deadly pathogen that causes tuberculosis (TB). TB infections often start out sculpting porous lesions in lungs, and they can make their way to the lymph node, blood, and other organs. The threat of TB is made worse by the recent occurrence of strains that are resistant to traditional treatments. One characteristic of the infection makes those frightening data a little easier to deal with: In 90 percent of the two billion people with *M. tuberculosis*, the mycobacterium will lie latent. The other 10 percent are likely to develop TB in their lifetimes.

How is it the man overheard on the street falls into that unlucky 10 percent? A physician is likely to tell you that his immune system was somehow compromised—perhaps through drug abuse or malnutrition—and that the risk of contracting the pathogen (which is transmitted through the air) is higher among those living in crowded quarters. But if you ask why that particular man ended up with TB and not the guy sleeping next to him at the shelter—who also has a one-in-three chance of harboring the infection—your question is liable to be received with a shrug and a head scratch.

Genetics is known to have a role in some immune functions, yet no one knows why the TB organism remains happily latent in some and sets out on a course of destruction in others, killing three million people every year. (The current vaccine's effectiveness varies widely among adults and is not generally administered in the United States.)



COURTESY FLYNN

Macrophage vacuoles (red) serve as the main hosts for *M. tuberculosis* (green). In about 90 percent of infected patients, the macrophages are able to control the infection so that TB doesn't develop. Flynn wants to know how.

"It comes down to what happens between the host and the organism," says JoAnne Flynn, a PhD and an associate professor in the Department of Molecular Genetics and Biochemistry. To examine the host/organism interaction, she created a latent infection in vivo, no simple task. "We're trying to model something we don't understand," says Flynn. She and other immunologists don't know if the mycobacterium is replicating, morphing, or sitting still during those "latent" periods. They are pretty sure of a few things though, like the role that CD4+ T cells play in keeping TB infection at bay—or at least they used to be pretty sure. CD4+ T cells make a key cytokine (interferon gamma). That cytokine tells the macrophage housing the *M. tuberculosis* to stop being such an accommodating host and to kill the pathogen by releasing nitric oxide. It appeared that if you could use CD4+ T cells to keep the macrophages activated, you could control the bug. Flynn decided to find out what would happen if she took CD4+ T cells out of the equation.

First she created a stable and chronic *M. tuberculosis* infection in mice; then she used antibodies to destroy their CD4+ T cells. Not surprisingly, the mice contracted TB and died. *Yet, somehow, their macrophages were still activated.* It seems CD4+ T cells are necessary to prevent widespread infection but don't work alone.

These days Flynn is scratching her head a bit, but she has reason to be optimistic. She has a workable in-vivo model that's allowing her to decipher elements of the immune response, including the roles of other T cells. And she's convinced the only way to develop an effective vaccine is by first pinpointing exactly what's happening at this level—even if it means lots of head scratching. ■

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