Harnessing the healing force within

MEDICINE ■ The chemicals that the body produces to repair injuries may become the newest weapons in the medical arsenal

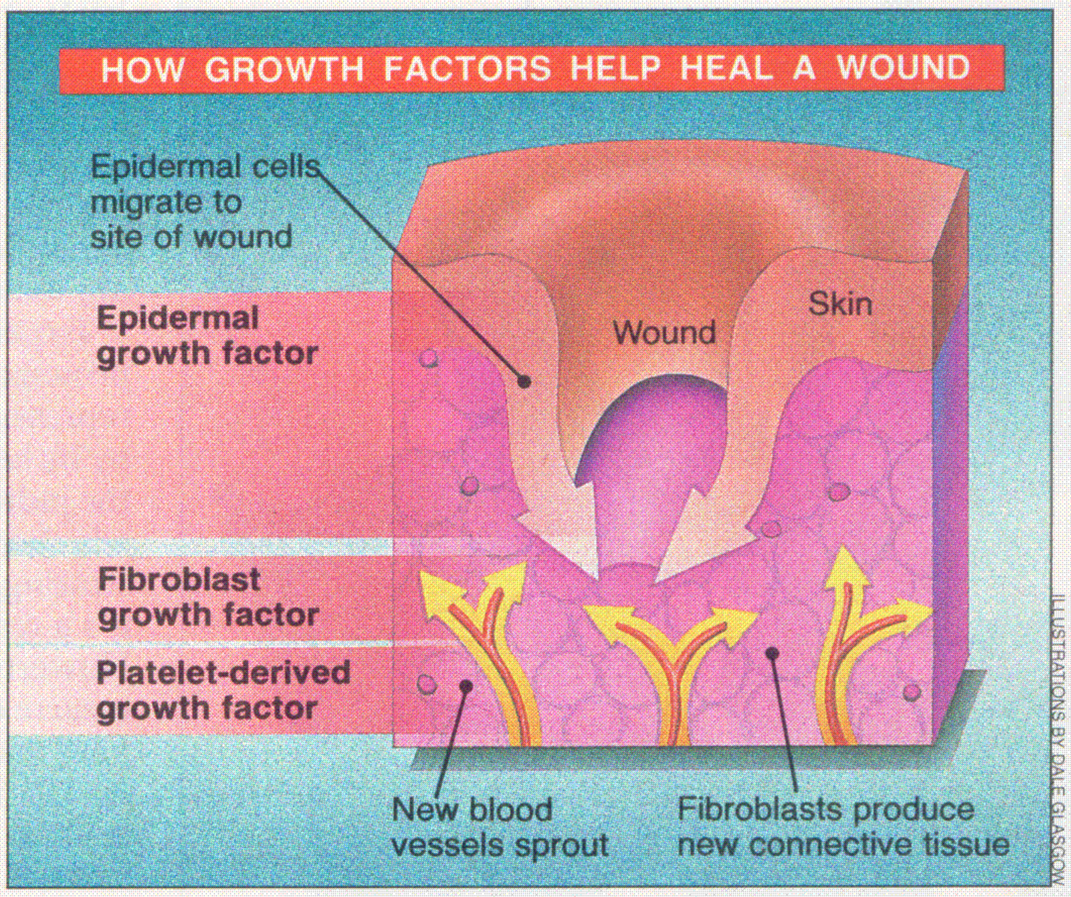
■ A man suffered a chemical burn to his eye that was still unhealed five weeks later.

■ A victim of radiation poisoning couldn't make enough white blood cells to fight off bacterial infections that threatened his life.

■ A diabetic was advised to have his leg amputated when a festering sore on his sole became gangrenous.

In each of these cases, a new class of substances came to the rescue. The patients are among a thousand or so experimental subjects to receive growth factors, the very chemicals the body uses to heal itself. "With these tools in hand," says Dr. Malcolm Moore, a blood specialist at Memorial Sloan-Kettering Cancer Center, "we can literally order up new cells to replenish damaged ones."

Although growth factors were first detected in animal embryos more than 40 years ago, research was hampered by the minute quantities of these small proteins that could be isolated and purified. But with the coming of biotechnological techniques to mass-produce human proteins in genetically altered microbes, scientists are now beginning to understand how growth factors work and how they can be harnessed for healing. Today, some 30 growth factors have been identified; each has a specific ability to make certain cells in the body—such as skin, nerves and bone—divide more quickly. Some also encourage cells at the site of an injury to block hemorrhaging, fight infection and recruit new building materials. Ultimately, they might be used to treat degenerative diseases of the brain, gastric ulcers and male infertility—to name a few possibilities currently being explored in animal experiments.



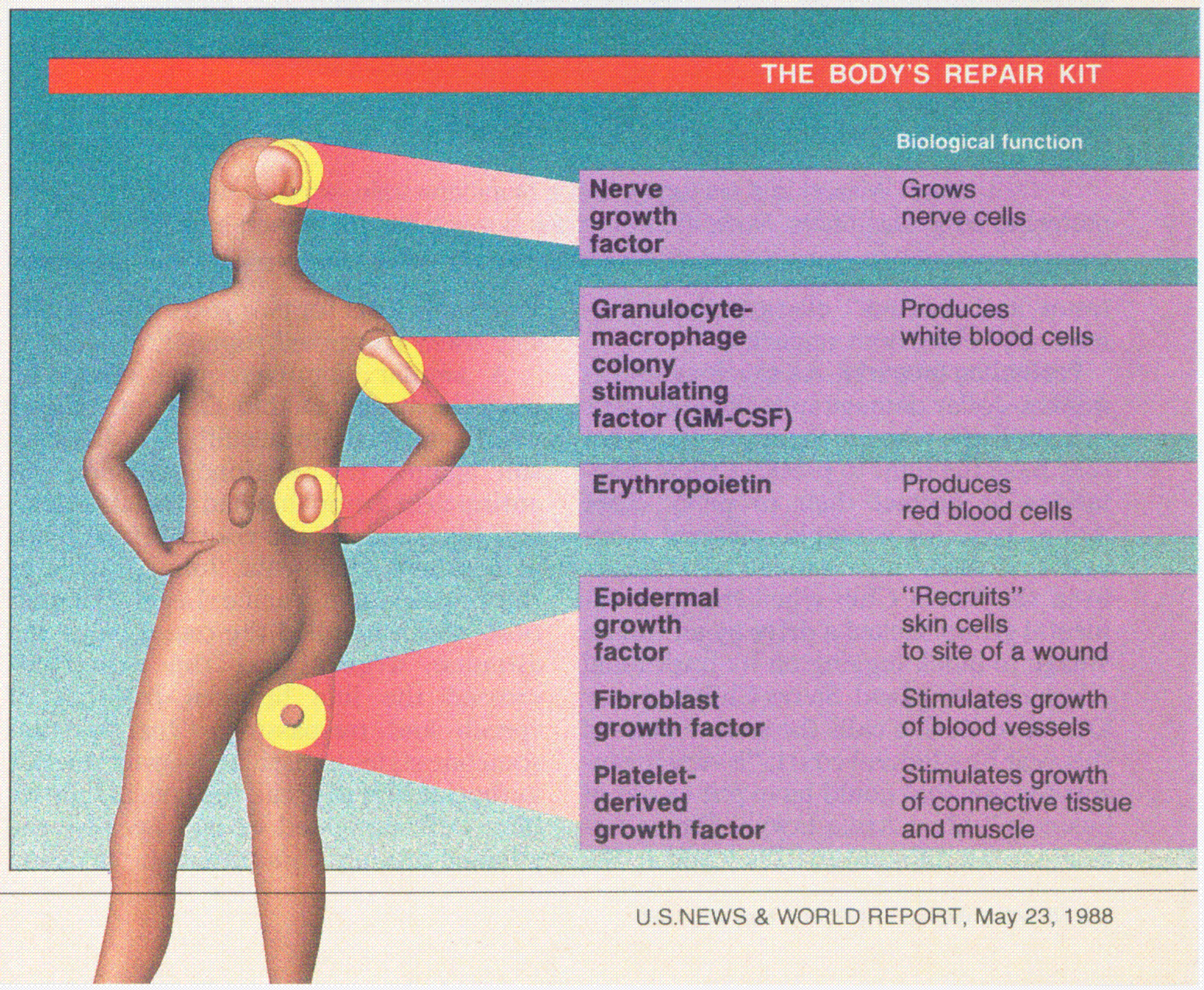
Growing your own blood. Closest to routine clinical use are the blood growth factors, which have been shown to dramatically increase a patient's supply of red or white blood cells. Anemics or patients who have lost blood in surgery might be able to avoid the need for transfusions; surgical patients might even be given the red-cell growth factor, called erythropoietin, ahead of time to produce blood that could be drawn and stored for later use.

The growth factor called GM-CSF that boosts a patient's white-cell count may have even more-dramatic clinical consequences—"as revolutionary as antibiotics," says Dr. David Golde, chief of the division of blood diseases and cancer at the University of California at Los Angeles. White cells, which are produced in the bone marrow and which the body needs to fight off infection, are often severely reduced in patients who have undergone bone-marrow transplants or whose marrow has been damaged by radiation or by the toxic side effects of cancer chemotherapy.

Dr. Robert Gale, associate professor of medicine at the University of California at Los Angeles, gave GM-CSF last year to eight Brazilians who were accidentally exposed to radioactive cesium from a dismantled medical device. Four are still alive and have returned home, free of infection. Gale believes more would have died had it not been for GM-CSF. "All their blood counts shot up promptly in response to the treatment," he reports, "and we know the fewer days your white-cell count is low, the greater your chance of survival."

Cancer patients given GM-CSF or several closely related compounds may be able to tolerate higher doses of anticancer drugs, which could translate into a higher cure rate. And there is some hope that these growth factors may benefit AIDS patients, whose white blood cells are destroyed by the virus.

None of these factors is yet approved for general use. But "most of the largest biotechnology companies are avidly pursuing growth-factor products," says Ste-



phen Buell, an analyst at Kidder, Peabody & Company in New York City. The total market for growth factors is estimated at several billion dollars a year by the end of the century.

The growth factors involved in wound healing are of particular commercial interest. Some 3 million Americans—especially the elderly and diabetics—suffer from serious nonhealing wounds such as bedsores. Promising initial successes have been reported in using growth factors to heal not only these skin ulcers but also eye injuries and surgical incisions made in corneal transplants.

Recent clinical trials by Ethicon, a division of Johnson & Johnson in Somerville, N.J., indicate that epidermal growth factor, which stimulates skin cells to multiply, heals deep ulcers of the skin in half the normal time. Epidermal growth factor was first discovered in the salivary glands of animals—which may explain why animals instinctively lick their wounds.

Repairing injured eyes. Chiron, a biotech corporation in Emeryville, Calif., is also exploring the compound's use in repairing injuries to the surface of the cornea that refuse to mend. In tests on 60 patients, one third of the eye injuries healed completely, and one third partially healed. The clinical trial was stopped when a few patients reported pain. But according to Dr. Richard Eiferman, the ophthalmologist in charge of testing the compound at Kentucky's University of Louisville Medical School, the problem will be easily overcome by altering the dosage and method of application. "This was a tremendous result for a first trial," he says. "Some of these eyes were the worst we'd ever seen and had defied all standard treatments."

Dozens of separate factors choreograph the intricate steps of clotting, the regeneration of blood vessels and the growth of new skin cells and a supporting framework of collagen. So the most effective results may be obtained by using a combination of growth factors and applying them in a sequence that closely mimics the natural process. In one experimental treatment, bandages are soaked in a "cocktail" made up of several different growth factors and applied directly to the wound. Dr. David Knighton, a surgeon at the University of Minnesota Hospital and Clinic, has used the treatment with an 85 percent success rate on 800 patients with open sores that had remained unhealed for an average of two years. Many of the patients were originally referred to him for amputation owing to a longstanding wound that had become infected.

Researchers believe that the major natural function of growth factors is to orchestrate the development of new tissue in the embryo. The first growth factor was discovered by Italian biologist Rita Levi-Montalcini, working under primitive conditions in her bedroom during World War II. In a series of elegant experiments, she was able to prove that chick embryos produce a substance that makes nerves proliferate.

Growth factors play a more limited role after birth—mainly directing the regrowth of tissue following an injury. The very specific action of growth factors is what makes them such potentially powerful medical tools. "Cells use growth factors to communicate with each other over microscopic distances," explains Dr. Robert A. Weinberg, a biologist at the Whitehead Institute for Biomedical Research in Cambridge, Mass. These chemical signals are then picked up by special receptors on neighboring cells, which transmit the information to genes in the interior. In this way, growth factors produced by one cell can alter the genetic program of another, causing it to divide more quickly, migrate toward the center of a wound or even mature into a different type of cell.

Cautious optimism. For all the progress, researchers have decades of work ahead. Scientists expect dozens of additional growth factors to be uncovered in the brain alone.

But the same researchers who caution against inflated medical expectations today anticipate extraordinary advances in the more distant future. "Once we figure out what all these growth factors do," says Weinberg, "it may be plausible to regrow whole organs that become diseased or damaged." ■

by Kathleen McAuliffe

SCOTT THODE—USN&WR

Both colonies of skin cells started from a single cell. EGF was applied to the one at right

Manufacturing human skin

Growth factors can be used to treat patients directly. But they're also being used in the laboratory to produce artificially grown human skin. Sheets of laboratory-grown skin are then applied to skin ulcers or second-degree burns to speed healing.

Dr. Howard Green of the Harvard Medical School starts with cells from the foreskins of circumcised infants. The cells, which naturally contain a high concentration of growth factors to begin with, are grown in a laboratory dish in the presence of epidermal growth factor (EGF). When applied to the wound, the sheets protect the site of the injury and provide a rich source of growth factors to accelerate the body's natural healing process.

Applications
Speculative—might eventually be used in regrowing damaged brain or nerve cells
Helping bone-marrow-transplant patients and radiation victims fight off infection; counteracting damaging side effects of cancer chemotherapy
Treating anemia; replenishing blood lost in surgery
Treating corneal ulcers, nonhealing sores; speeding healing of skin grafts and corneal transplants
Treating skin wounds and burns
Treating skin wounds