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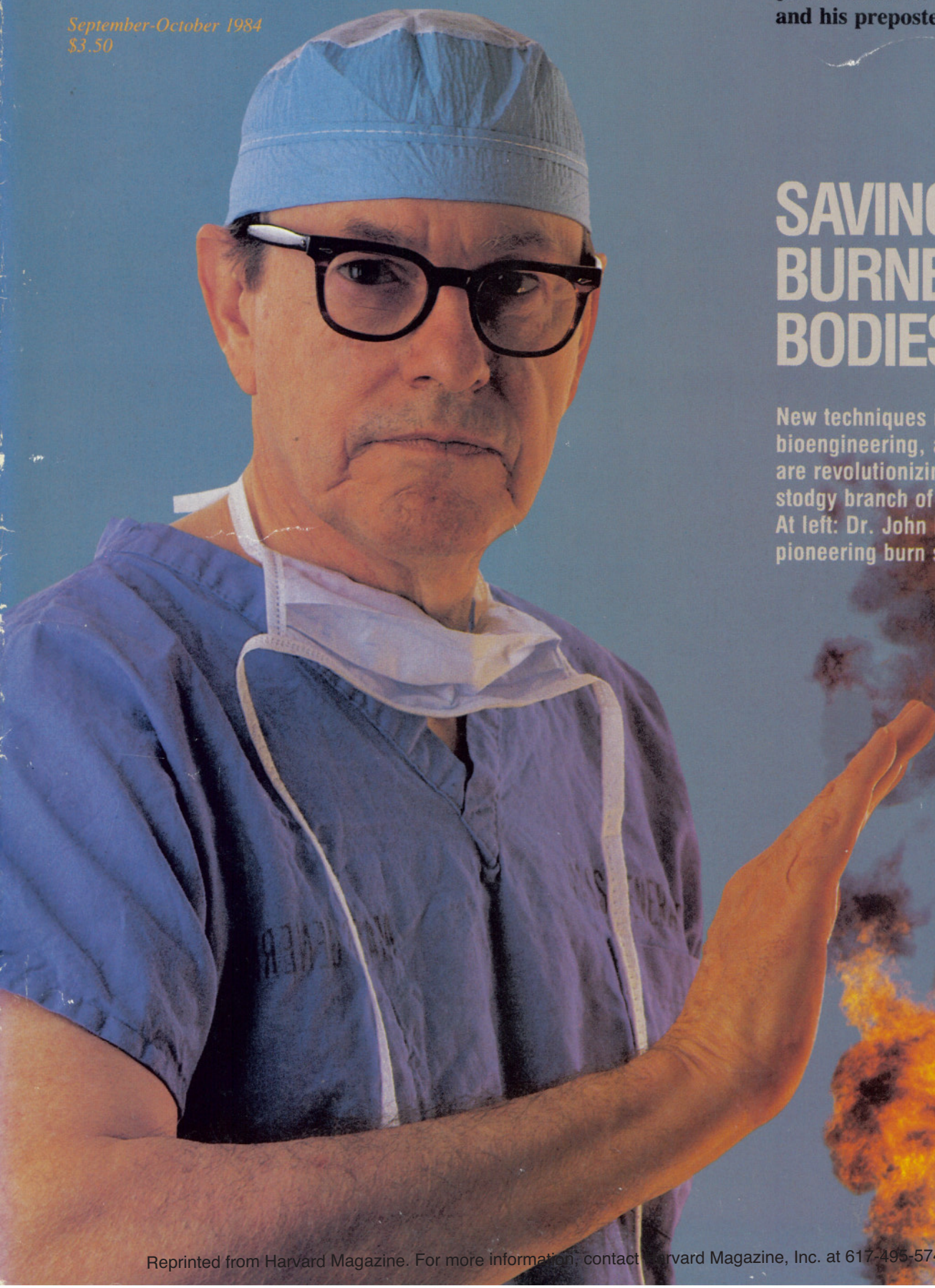
SAMUEL BEER: Memoirs of
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SAVING BURNED BODIES

New techniques in surgery,
bioengineering, and cell culture
are revolutionizing a formerly
stodgy branch of medicine.
At left: Dr. John F. Burke,
pioneering burn surgeon.







At left: Rescue operations at Boston's Cocoanut Grove, 1942. The nightclub disaster, which took 491 lives, helped alert physicians to the pressing need for changes in burn trauma management.

TRIED IN THE FIRE: NEW TREATMENTS FOR MASSIVE BURNS

by S. B. Sutton

A "full-thickness" burn, searing tissue down to the fat layer, is probably the most devastating injury a person can sustain: Even when the victim survives the wound, he may live with its consequences for the rest of his life. In the first 36 to 48 hours shock is the most immediate danger. Damaged capillaries pour plasma, water, electrolytes, and proteins into the wound, draining the rest of the body. The metabolic system goes haywire. Kidney failure, anemia, malnutrition, and pulmonary insufficiency are among the secondary hazards. Huge caloric intake

is vitally needed, but most victims are in no condition to eat. In the words of Dr. John F. Burke, Massachusetts General Hospital's top burn man, these patients are "sick as hell."

Most life-or-death crises are resolved within days, but a burn victim's life may hang in the balance for weeks. Burn patients require the longest and most costly hospital stays; many emerge disfigured or disabled.

An estimated 130,000 Americans are severely burned each year, and 10,000 of them die. But the survival rate is improving dramatically as a result of recent changes in therapy. In the Fifties

and Sixties, Dr. Burke was a leader in reformulating the traditionally vexing problem of massive burns, emphasizing the full extent of the victim's sickness and reordering treatment priorities. With M.I.T.'s Ioannis Yannas and others, Burke went on to pioneer the immediate closure of large burn wounds with "artificial skin"—a synthetic membrane that allows a patient's dermal cells to regroup over his wounds, creating a skin layer that is later covered with grafted epidermis. Since the first application to humans, announced in 1981, the technique has been used in about fifty cases.

Burke and Yannas are now testing a "Stage II" technique that promotes the generation of epidermal as well as dermal cells, obviating the need for follow-up grafts. They expect to begin trials with humans this fall.

Working independently, other high-technology researchers are developing alternate forms of substitute skin. A team of Boston doctors made headlines in August with the announcement that laboratory-cultured epidermal tissue had been grafted successfully in a case involving two young brothers burned over 95 percent of their bodies. Dr. Howard Green, Higgins professor of physiology at Harvard Medical School, took samples of each boy's epithelial cells and cultured them into sheets of delicate tissue within three weeks. Surgeons sutured the tissue over the boys' wounds in a series of operations, replacing half their original skin. Green and his colleagues believe their technique is the best that has yet been tried, because it yields ample amounts of tissue and requires no follow-up grafts of epidermis.

Researchers may differ over the best way to make second skin, but all base their work on the finding that human skin can regenerate itself—an ability once thought to belong only to lower animals, like salamanders or worms. The implications go beyond burn research, and suggest that it may eventually be possible to engineer the regeneration of other tissues or organs that are damaged or lost.

Burn treatment is a field of intense activity today, but in no other medical branch has progress been so long in coming. From the time of Prometheus onward, topical preparations, full of noxious ingredients, remained the conventional treatment for burns of all types. Even into this century, doctors and medical workers harmed the victims of burn injuries more than they helped them.

In the spring of 1928, a fourth-year Harvard medical student named Oliver Cope stood by in the Mass General emergency ward to help minister to some thirty casualties of an oil-tank explosion. After stripping away dead epidermis, MGH medical workers proceeded to soak the wounds in tannic acid. Cope watched in horror as one victim after another died of dehydration. He wrote later, "It was evident even then that the priorities were off balance." Nevertheless, this unwholesome regime obtained for another decade. Cope meanwhile turned his attention to the endocrine glands and made medical history by locating the elusive parathyroids.

The threat of war and a federal grant (a rare thing in those days) revived Cope's curiosity about burns. In 1941

he and Drs. Bradford Cannon, Francis Moore, and F.W. Rhineland, all of Mass General, began investigating the physiology of burns in the hope of improving treatment and saving lives, especially in disaster situations. They based their studies on the theory that care of the surface wounds ought to be simplified to allow medical personnel the time to attend to the administration of fluids. In a matter of months they rewrote the book on wound treatment, throwing out tannic acid, which they demonstrated to be toxic, and replacing it with bland

In a few months a handful of doctors rewrote the book on burn treatment.

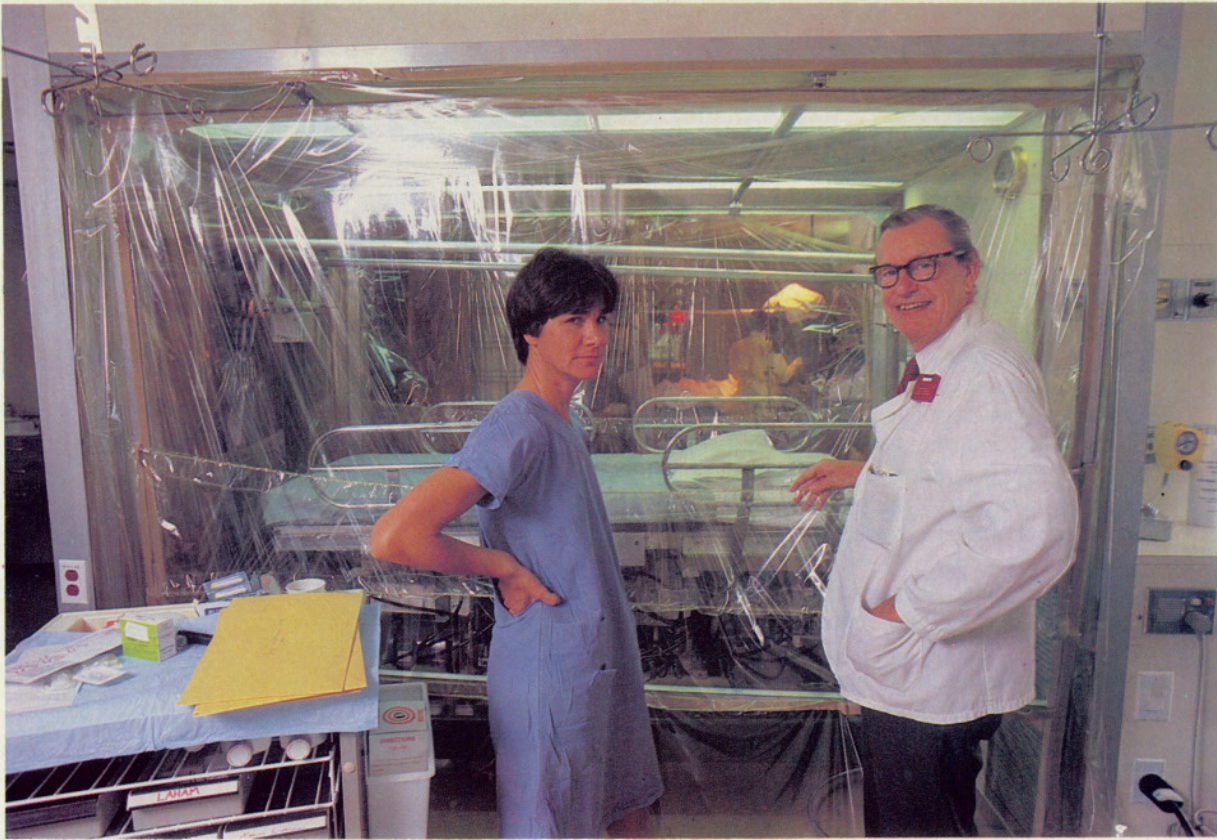
ointment, sterile dressings, and pressure bandages; they advocated infusions of blood plasma, glucose, and saline solution to patients demonstrating symptoms of burn shock. These recommendations were still fresh and unrefined when Providence intervened impolitely to test them.

On Saturday, November 28, 1942, around 10 p.m., fire broke out at the Cocomanut Grove, a Boston nightclub. If this was not the war-related crisis for which Mass General had been preparing, it still qualified as a disaster of tragic proportions. Four hundred and ninety-one people perished as a consequence of the blaze, many of them caught inside the building. The nightclub was a fire trap. Subsequent inspection implicated, among other things, a jammed revolving door. The Boston fire code was soon revised; this is why the revolving doors at the Ritz Carlton Hotel bear the ominous message: NOT AN ACCREDITED EGRESS DOOR.

Police and firemen at the scene ordered victims transported to Boston City Hospital, but facilities there soon became exhausted, so another group was diverted to Mass General. Acting on notification to expect a large number of patients, the hospital summoned staff and volunteers from their Saturday evening revels; Cope appeared in his tuxedo. Patients began arriving at 10:30. By 12:45 a.m., Sunday, 114 casualties had been received; of these, 75 died en route to the hospital or soon after arrival, in most cases from asphyxiation. Of the 39 MGH patients who survived until 1:30 a.m., seven died during the following week, leaving 32 survivors in the hospital. (One committed suicide several weeks after his discharge.)

Disasters sometimes create exceptional medical research opportunities. The Cocomanut Grove fire animated an array of research efforts, among them psychiatrist Erich Lindemann's classic study, "Symptomatology and Management of Acute Grief" (American Journal of Psychiatry, September 1944). As to burns, the findings of most immediate significance involved the management of fluid balance. Observation of the Cocomanut Grove casualties—thirty of whom had suffered clinically significant burns—suggested that the quantity of fluid given should be proportionate to the surface area burned. A surface-area formula was devised to anticipate the fluid needs of a burn victim, and a schedule of administration was designed. Cocomanut Grove further dramatized many problems in burn treatment and left some MGH physicians who had witnessed the scene with an almost obsessive desire to set them aright. Meanwhile, a bigger research opportunity was in progress. World War II gave to medicine substantial experience with trauma, includ-

Overleaf: The photograph of the Cocomanut Grove fire is courtesy Wide World Photos; the photograph of the charred picture and flames is by Peter Jones.



Mass General's new burn center, "the most technically advanced in the nation," opened in July. Intensive-care beds are enclosed by thermal plastic; air is constantly changed to remove bacteria. In the foreground, head nurse Elizabeth Dickerson and Dr. John F. Burke, chief of trauma service. In the background, a burn-unit team performing an emergency procedure.

ing burns; it became apparent, for example, that all dead tissue should be removed as soon as possible, since it acts as a culture medium for bacteria. Still, in the 1950s, most people who suffered third-degree, or full-thickness, burns over 40 percent of their bodies died.

Though Cope and Moore had drawn on wartime experience to demonstrate the wisdom of cutting away dead tissue from third-degree burns and closing the wound as soon as possible, the risks of the operating room were such that practice dictated the postponement of surgery until the patient had been stabilized. During the wait the wound deteriorated, and the hazards of infection accumulated by the hour. Daily dressing changes meant excruciating pain for the patient. But as medicine became more efficient in managing the early difficulties of burn shock, the time between accident and surgery gradually diminished.

Which brings us, finally, to the subject of skin, the real star of this article. The old way to close a burn wound was to harvest skin from an unburned portion of the body and graft it to the damaged areas. But people who have sustained 50-percent-or-greater burns do not have enough healthy skin to go around. Such hapless individuals used to face a series of operations, the surgeons waiting for new healthy skin to make itself available and repairing the damage piece by piece—a painful patchwork process that prolonged susceptibility to infec-

tion and made for lengthy hospital stays. Having solved most of the major problems of shock by the late 1950s, a new generation of Harvard physicians at Mass General determined to develop a clinical program based on the prompt excision of necrotic tissue and immediate wound closure. Burke, former head of the MGH Shriners Burns Institute, now Helen Andrus Benedict professor of surgery and chief of the MGH Trauma Service, led the new efforts, although Cope was very much the *éminence grise* in the background. The initiative got a shot in the arm in 1962, when the Shriners Hospitals for Crippled Children decided to locate their first Burns Institute at Mass General. (The institution's long record of work on burns attracted the Shrine; when the representative of the Shrine's Burns Committee paid his first call on the hospital, he found the walls of Cope's office papered with maps and diagrams of a burns research unit for which the doctor was hoping to raise federal support.)

Immediate wound closure of large-scale burns depended upon the availability of skin, or a suitable substitute. Therefore, in 1962, the MGH launched a search for artificial skin. Since no one expected such stuff to be rolling off the assembly line right away, however, a simultaneous effort was made to create a stockpile of skin for those cases presenting a shortage of healthy autograft tissue. Burke's team accomplished this feat by establishing, in 1969, the world's first frozen skin bank, wherein is deposited skin harvested from cadavers. The disadvantage of cadaver allografts lay in the patient's rejection of them—just as recipients of alien kidneys or hearts try to expel *them*—and in the consequent need for immunosuppressive drugs. Though this seemed dangerous at a time when the patients needed their immune systems to fight infection, it was reasoned that the risk of infection with a large, open burn wound was greater than that of

Skin hunters

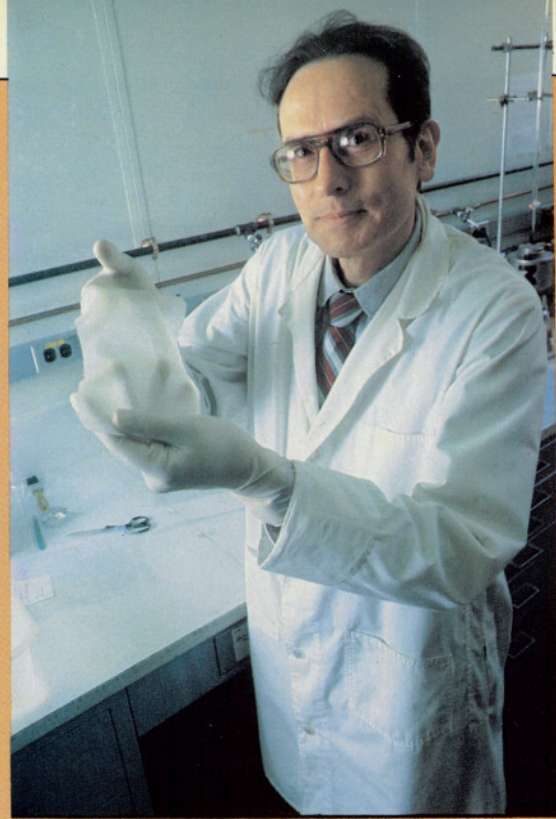
In 1969, after unavailing efforts to develop a synthetic skin with which to close burn wounds, surgeon John F. Burke turned to Ioannis Yannas, professor of polymer science and engineering at M.I.T. Born in Athens, Yannas had graduated from Harvard in 1957 and taken advanced degrees from M.I.T. and Princeton. As a bioengineer, he was especially interested in devising ways to repair connective tissue, using the tough fibrous proteins called collagens.

With doctoral candidate Chor Huang, Yannas began with the idea that collagen, combined with a glycosaminoglycan (GAG) to improve its toughness, could make a single-layer membrane strong enough to provide an effective wound covering. In adding GAG, says Yannas, they were doing the right thing for the wrong reason. It didn't increase the strength of the membrane, but it had a critical influence on its rate of degradation.

Degradation—the metabolic interaction of the man-made membrane with the enzymes in a wound—proved a key process in developing “artificial” skin. Yannas, Huang, and Dr. Philip Gordon realized that an effective wound covering should dissolve at a rate commensurate with the rate at which the body regenerates skin. Collagen by itself broke down too fast, which made for an ineffective graft; GAG slowed degradation to an acceptable level.

Because their highly porous collagen-GAG membrane wasn't strong enough to take sutures, or thick enough to keep the wound clean, Yannas, Huang, and Gordon added a second layer of rubbery silicone plastic. That produced “a sandwich strong enough to be handled by a surgeon's hands,” says Yannas. By 1979 Burke had specimens from Yannas's lab and was experimenting with human implantation.

Yannas, Dr. Dennis Orgill, Eugene Skrabut, and Burke are now working on a new type of substitute skin that generates its own epidermis. “Stage II” skin cannot be stored, but it can be created quickly—in



JIM POZARIS/GAMMA-LIAISON

Ioannis Yannas with a sample of artificial skin.

less than two hours. To prepare a Stage II graft, researchers harvest the youngest epidermal cells from a small area of healthy skin (dime-sized in a lab animal). In a centrifuge, the cells are then seeded into the collagen-GAG layer of Stage I skin. Because the cells cannot live long outside the body, the graft is implanted immediately.

In a few days the young epidermal cells move upward toward the interface of the collagen-GAG layer and the outer covering of plastic. In ten to twelve days a new epidermis is completely formed, and the plastic layer is ejected spontaneously. The new skin matures over the next few months, obviating the need for another series of grafts to implant epidermis. Yannas and Burke say Stage II skin will be ready for human implantation this fall.

a closed wound with the drugs. Indeed, the MGH did not lose a single immuno-suppressed patient due to infection, and the death rate from massive burns dropped impressively during the 1970s.

But cadaver allografts were always viewed as an imperfect solution. The transplanted skin was temporary and was removed as soon as the patient developed sufficient autograft donor sites. By contrast, the guiding thought behind the search for artificial skin was to find a substance that would be compatible with the wound bed and, thereby, eliminate rejection and the need for the second set of grafts. Early laboratory tests with synthetic materials were discouraging but not entirely futile, for Burke and his team were persuaded to abandon the concept that an artificial skin had to be made from an inert, nonreactive substance.

In 1964 Dr. Peter Morris joined the group, and its research picked up momentum. By 1966 the team con-

cluded that a successful membrane could be made from collagen (a supportive protein found in skin and other connective tissues) plus a glycosaminoglycan (also a connective tissue substance). But, though they had their ingredients, the researchers could not create a new material. In 1969, when frustration was beginning to run high, Burke sent up signals for help at M.I.T. That December, Professor Ioannis Yannas of the Mechanical Engineering Department called to say he was interested in biomaterials. The two institutions went into partnership. By 1973 the concept of a bilayer membrane had been developed, and six years later artificial skin was ready for trial on humans. In April 1981 Burke and Yannas made the stunning announcement that the new material had been used successfully in treating ten patients who had sustained third-degree burns over 50 to 90 percent of their bodies.

In three of these patients, who had developed infections before arrival at the hospital, Burke believed arti-

ficial skin might have made the difference between life and death.

The dermal, or lower, layer of the material is made from cowhide collagen and a glycosaminoglycan obtained from shark cartilage—a detail Burke wishes he had never leaked to the press, because the substance can be extracted from many sources; the chemical company that supplied him just happened to get theirs from sharks. The components are fabricated into a three-dimensional structure resembling the connective fibers of normal dermal tissue. When it is implanted on the wound, cells migrate into the man-made scaffolding and begin to produce more collagen; the synthetic tissue breaks down as it is replaced by the patient's own "neodermis." Artificial skin's exterior layer is medical-grade Silastic, a rubbery plastic, which is removed after a few weeks when the patient has generated healthy epidermis for grafting.

A handful of graduate students are making the skin in Yannas's lab, at a weekly rate of one to three sheets about the size of this page. Marion Laboratories of Kansas City, Missouri, is also licensed to produce it. Officially the skin is still an experiment. Detailed control studies must be assessed before the Food and Drug Administration approves distribution.

About fifty patients at Mass General and the MGH-Shriners Burns Institute have received artificial skin. Burke and Yannas consider it a success. Four years of experience show that humans do not reject it. The material, says Yannas, has proved effective in keeping wounds bacteria-free and in controlling moisture loss. The ability to wheel a patient into the operating room within hours of arrival, plane away dead tissue, and promptly close the wound reduces contracture and scarring. The substitute skin is easy to store for emergency use.

Although subsequent autografts of epidermis involve a much less traumatic procedure than grafting split-thickness skin containing dermis, Burke and Yannas are staking their hopes on a one-step skin replacement that generates epidermis autonomously (see box). "Stage II" skin cannot be stored, but reportedly can be prepared and implanted within four hours. After almost three years of testing with animals, Burke and Yannas say they are ready to begin trials with humans.

In essence, Burke and Yannas are utilizing a burn victim's body as a bioreactor to grow new tissue. Others, including Harvard Medical School's Howard Green and M.I.T.'s Eugene Bell, are taking a different tack. They are culturing human skin in their labs.

Earlier researchers tried that, but failed to obtain graft-sized quantities. Independently, Green and Bell succeeded by recognizing the importance of fibroblasts—interior skin cells that help produce collagen.

In contrast to Burke and Yannas, who start by regenerating the inner layer of skin, Green cultures the outer layer. Working with two young surgeons, Nicholas O'Connor and G. Gregory Gallico III, he provided epithelial tissue for six burn victims between 1980 and 1983. These test grafts, made from the patients' own cells, covered up to six percent of body surface.

In July 1983 came a test of a different order. Two Wyoming boys, burned head to toe, were sent to the Shriners Burns Institute by a Denver doctor who knew of Green's work there. Jamie Selby, five, and his brother Glen, six, had put paint on their naked bodies and were

using gasoline to remove it when they came in contact with a flame. Third-degree burns covered 83 percent of Jamie's body and 89 percent of Glen's. "I don't think anyone with burns of that size has ever survived," says Gallico. His team had not anticipated treating such massive wounds. "But since these boys had no other hope for survival, we agreed to try."

Starting with postage-stamp-sized biopsies from the boys' armpits, Green cultured graftable sheets of epithelium within three weeks. In the interim, tissues destroyed by the third-degree burns were pared to the muscle layer, and the wounds closed with Burke-Yannas membranes and cadaver skin from the MGH-Shriners bank. Over a five-month period, these temporary grafts were removed, and gauze-backed sheets of cultured epithelium were sutured over half the boys' bodies. Green provided a square yard of skin for each patient. In the August 16 issue of the *New England Journal of Medicine*, Gallico reports that successfully grafted epithelium grows to normal thickness, and is smooth and supple. Like Burke-Yannas skin, it lacks sweat glands and hair follicles. "We believe a dermis may develop under the new covering," says Gallico, "but in fact a dermis may not be absolutely necessary."

Jamie Selby is now in school again. Glen needs grafts on his back, but is mobile. How do they look? "They're significantly scarred, much like other burn patients," says Gallico. "To me," he adds, "they look great."

This summer Mass General opened "the most technically advanced burn center in the nation." Substitute skin may be its most important offering, but is only one of the developments that make care at the center state-of-the-art. The new ward can handle ten patients, including four in intensive care. Each critical-care bed is enclosed in transparent thermal plastic, and equipped with a laminar-flow unit that constantly changes the air, keeping the area free from bacteria. Beds are within easy reach of each other, increasing the mobility and efficiency of medical workers. An experimental hydraulic bed makes easier the task of moving a patient to dress his burns or change his sheets. Knowledge and treatment have come a long way since Oliver Cope ministered to his first burn patients.

At the time of Coconut Grove, 25- to 30-percent burns were usually fatal. Today, half the victims of 80-percent burns can survive. Like most medical advances, it has been a long haul, a matter of bringing one problem under control and proceeding carefully to the next. The work has profited from progress in surgery, immunology, anesthesia, biochemistry, bacteriology, and an essential contribution from engineering. And the search continues. Burke pursues studies of the metabolic alterations in burn patients with the aim of developing an optimal nutritional program. The quest for the best "second skin" seems certain to attract more cell-culture researchers. Yannas and others envision a time when man-made matrixes can help other parts of the body to regenerate. As usual, science fiction is much less astonishing than the real thing. □

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