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More Than Skin Deep: [Dr. D. Martin Carter]

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"And the master-word is work . . ."
From the essay, "The Master-word in Medicine."
–WILLIAM OSLER, 1903

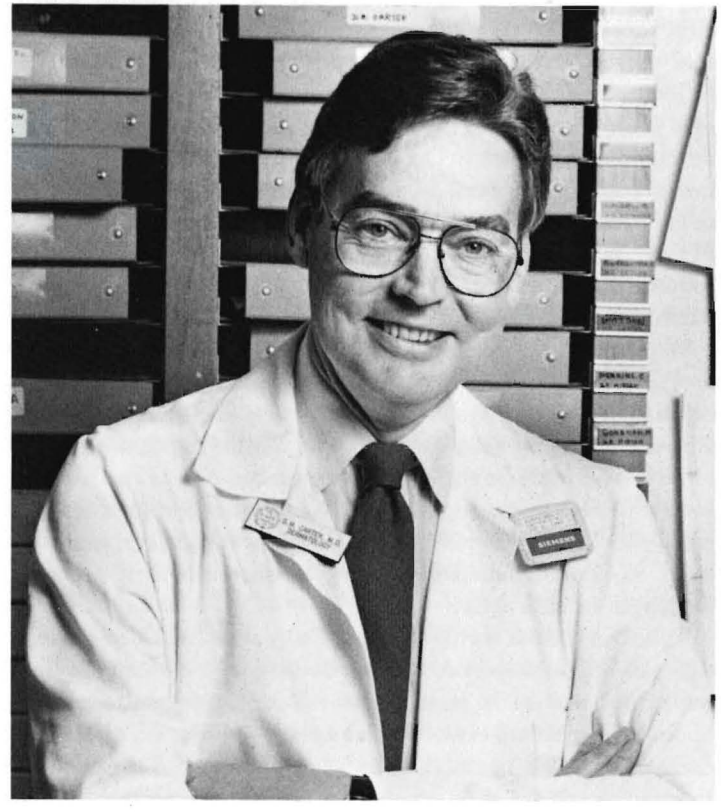
More Than Skin Deep

A child falls and scrapes his knee. In a few days the injured spot heals with a fresh layer of healthy skin, and the protective barrier to environmental insults is restored.

Another child, not so lucky, awakens every morning with raw wounds on his cheeks caused by the pressure from his pillow during the night. That boy, born with a single defective gene that predisposes him to extensive blistering, is currently a patient at The Rockefeller University Hospital. His condition, like those of others for whom the skin's normal protective functions have failed, is being studied and treated by researchers of the laboratory for investigative dermatology, under the direction of Professor D. Martin Carter.

Dr. Carter came to Rockefeller from Yale University in 1981. An innovator and ardent proselytizer in what until recently has been an underpopulated and relatively unexplored science, he has in four years established one of the most comprehensive programs of dermatological research and treatment in the country, based at Rockefeller with associated services at New York Hospital-Cornell Medical Center and Memorial Sloan-Kettering Cancer Center.

The research in Dr. Carter's laboratory has as its overall focus a quest for deeper understanding of how the external environment interacts with genetic and other internal influences to modulate the skin's responses. "We study these interactions," he says, "at the cellular level, the molecular level—the level



D. Martin Carter

of chromosomes and genes—and the biochemical level; in the test tube and in the people we treat."

On the ward, he and his colleagues are applying new advances in research, from his laboratory and others, to some old and persistent problems that affect the skin: psoriasis, cancer, ulceration, epidermolysis bullosa (the boy's disease), Fanconi anemia, pemphigus, aging.

THE HAZARDS OF LIGHT AND AIR

The complexities of the skin's interactions with the environment have been observed for a very long time. Thirty-five hundred years ago people in India had discovered that extracts of certain plants such as figs and wild parsnips, rubbed on the skin or eaten, modifed the effects of vitiligo, a condition in which large areas of the skin lack pigmentation. Scientists now know that these plants are among a group that contains compounds called psoralens, which react to light. At Yale, where he went as a young dermatologist and subsequently earned a Ph.D. in developmental biology, Dr. Carter participated in some of the first studies of the mode of action of psoralens administered in conjunction with ultraviolet irradiation. The technique, called PUVA, is used in the treatment of psoriasis, a common and sometimes serious skin disorder characterized by large, inflamed patches and heavy scaling.

A complicating side effect of PUVA, which the Yale study determined and alerted the medical community to, is that it can damage chromosomes. It can interfere with the activity of DNA, the genetic material contained within the chromosomes of cells, and increase the risk of skin cancer, just as can happen with repeated, excessive exposure to sunlight. To minimize the risk, Dr. Carter helped design psoralen blood-level tests in order to limit irradiation to periods when the drug is most accessible in skin cells.

Following those initial studies, Dr. Carter began to explore the particular properties of psoralens as a tool for studying basic cell behavior. In research that has continued at Rockefeller, he and other members of his laboratory use PUVA to induce damage to cells in culture in order to observe and characterize the ways in which cells go about repairing themselves.

Arthur Balin using the computer to analyze data on the effects of oxidative stress on cells in relation to his studies of the process of aging.

"We want to find out what kinds of repair mechanisms cells have," he explains. "Are they more efficient at some times than at others? Are some parts of DNA more protected or more susceptible to injury? To help answer such questions, Peter Ross, one of the colleagues who came to New York with me from Yale, has been examining specific, defined pieces, or sequences, of DNA, something we can do now that we know how to clone genes. Our aim is to provide a critical test of whether selective DNA repair in fact exists, and, if so, to quantitate it. This kind of information should help us understand more about processes like carcinogenesis."

Like sunlight, oxygen is an environmental agent vital to life. But oxygen and the products of oxidation can damage cells unless they are detoxified by protective mechanisms. Reactive oxygen molecules are continually produced within cells by respiration. Arthur Balin, who also first worked with Dr. Carter at Yale, uses oxidative stress as a model system for studying the process of aging, based on the theory that cellular deterioration by oxygen is an underlying cause of aging.

"Arthur and I got together through his interest in aging and mine in DNA damage and repair," says Dr. Carter. "Since coming to Rockefeller, we've been able to set up methods for exploring the consequences of oxidative stress by growing skin cells under various concentrations of oxygen. This hasn't really been done before in a systematic way."

"We're using human cells of all ages—the youngest from a ten-week fetus and the oldest from a person over ninety—and from normal subjects and patients with inherited defects of DNA stability," Dr. Balin says. "And we've been discovering some interesting things. For example, we've found that physiologic levels of oxygen regulate both the growth and the lifespan of human cells. We've also learned that different kinds of cells in the skin respond differently to different oxygen levels; they have different optimal growth requirements. What we normally think of as a bland environment—air with twenty percent oxygen concentration—is highly toxic to cells growing singly or in low densities. If you reduce the oxygen concentration, they grow better and their lifespan can be extended."

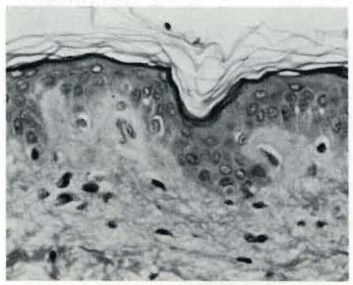
"So here we have a methodology that seems to be giving us

EPIDERMIS
A multicellular layer composed of scale-producing and pigment-producing cells.

DERMIS
Fibrocytes produce collagen and elastic fibers of supporting dermal matrix.

FAT CELLS

Photomicrograph of a section of human skin.



a way to learn more about fundamental factors in aging. At the same time," Dr. Carter points out, "we're putting the information about optimal conditions for cell growth to work clinically in the treatment of wounds."

LIVING BANDAGES

One of Dr. Carter's priorities when he came to New York was to set up clinical and experimental facilities for studying and improving the process of wound healing. The wounds his laboratory is concerned with are chronic and intractable.

"Leg ulcers plague the elderly, many of whom spend months bedridden in hospitals," he says. "They can result from a variety of causes, such as varicose veins or diabetes, or follow surgery or severe injury, affecting younger people as well. Relentless leg ulcers sometimes accompany sickle cell disease. Because of the trials we run, we get to see the very worst cases.

"Healing is influenced by a number of factors. Age is an important one, since old people heal more slowly than the young. The acid level in a wound area will affect the growth of infectious bacteria. The degree of moisture will influence the growth of new cells, but exactly how has been a subject of continuing debate. At one time, so little was understood about the effects of moisture that doctors used to joke, if the skin is wet, dry it, if it's dry, wet it, and if nothing works, put the patient in a tub of oatmeal. Our tests and others have shown clearly that healing is accelerated in a moist environment in which cells can move about freely."

Dr. Carter and his group test various medications and wound dressings currently in use or being developed, frequently at the request of the companies that make the products. They are applying Dr. Balin's findings, reducing oxygen concentrations around wounds to speed cell growth. They also are using cell technology to help develop new kinds of dressings.

One kind of dressing scientists find particularly promising, for both wounds and burns, is made from skin itself. The major obstacle in skin grafting from a donor is rejection by the immunological system. To eliminate the problem, some researchers, Dr. Carter among them, are experimenting with grafts made from the patient's own skin. A problem here is that if a large piece is needed, there is a risk that the graft may create a troublesome wound or disfiguring scarring. To get around this, Dr. Carter has adapted a technique introduced by Magdalena Eisinger of Memorial Sloan-Kettering and Jack Hefton of Cornell, in which skin is grown in culture from small starter grafts.

As he explains: "We've developed a device that raises a suction blister, a relatively painless and noninvasive procedure. In the blister, the epidermis, the outer layer of the skin, separates from the dermis. You can then cut off the top—the epidermis—and in two or three weeks, from a piece of tissue the size of a quarter, harvest a sheet of tissue several inches square. You place

this cellophane-thin epidermal membrane over the wound, and when the cells take up residence supporting skin cells begin to attach themselves underneath. It's been our experience that wounds healed this way tend not to reopen."

During the past three years, the laboratory has used the method successfully with a large number of patients whose wounds have failed to respond to any other approach. One current patient, so far responding well, is a forty-seven-year-old man crippled with arthritis, whose leg ulcers have delayed for four years the hip replacement surgery that will make it possible for him to walk again. Another is the boy with epidermolysis bullosa, or EB.

WHEN GENES GO WRONG

"It's a dreadful disease," says Dr. Carter. "A little irritation that you or I would hardly notice can produce extreme blistering in someone with EB. There are upwards of twenty forms of the disease, classified genetically according to where the blisters appear in the skin. The amount of scarring incurred depends on the depth of the blisters. The mild forms are, at best, aggravating nuisances. For people with severe forms, it's like being constantly burned from the day you're born. They're prone to massive infections and to cancer from the recurrent irritations. Their muscles atrophy, the mucous membranes in their respiratory and gastrointestinal tracts are often damaged so they have trouble breathing and eating, and their vision can be impaired. In the recessive dystrophic form, where the blisters—the bullae—go down into the dermis, the fingers and toes fuse, encased in scar mittens."

There is no cure for EB and the underlying mechanisms are still not understood. Current research implicates a malfunctioning of collagenase, an enzyme that breaks down collagen, the jellylike protein substance that comprises the major material of connective tissue and bone. As a result of the enzyme's defect, the epidermis doesn't anchor properly to the dermis in some types of EB.

EB is an "orphan" disease, a term used to denote conditions, usually rare ones, that don't get much attention or research money. Recently, the government passed an Orphan Drug Act to fund some trials, including a trial of the drug phenytoin (Dilantin) as a treatment for EB. First developed for epilepsy, phenytoin seems to inhibit collagenase activity. Dr. Carter is heading the project, which is being conducted at Rockefeller and seventeen other medical centers.

Fanconi anemia is another rare, inherited disease that affects the skin, as well as the blood, the kidneys, and the bones. FA victims suffer bone marrow failure, anemia, infection, hemorrhage, leukemia, and squamous cell cancer. They rarely live to adulthood.

While a postdoctoral fellow at Memorial Sloan-Kettering, Arleen Auerbach developed prenatal and postnatal diagnostic tests for Fanconi anemia. She studied cells from patients and from carriers of the genetic trait to determine their varying degrees of sensitivity to agents that can induce mutations or cancer. Her work contributed to a procedure that reduced the toxicity of bone marrow transplants, an important treatment for the disease. Since joining Dr. Carter's laboratory in 1982, she has developed a method for prenatal diagnosis in the first trimester of pregnancy. She is now studying the genetic heterogeneity of the disease with the goal of eventually mapping and isolating the gene responsible. Two years ago, in collaboration with Dr. Traute Schroeder of the University of Heidelberg, she established an International Fanconi Anemia Registry to gather patient histories including genetic, cellular, and clinical data, and information on the role of environment in the onset of the disease. She also provides prenatal counseling for FA families.

Because diseases that affect the skin can result from different underlying causes and involve different mechanisms, the scientists who work with Dr. Carter come from many fields, their arrival in dermatological investigations often serendipitous. Dr. Balin holds an M.D. and a Ph.D. in biochemistry from the University of Pennsylvania and Dr. Ross a Ph.D. in molecular genetics from Yale. Among the dermatologists based primarily at New York Hospital, Steven Cohen, a former olympic gymnast, is a specialist in occupational health, Scott McNutt is a pathologist, Philip Prioleau is a surgeon, and Rachelle Scott is a pediatrician whose interest in dermatology developed from

Arleen Auerbach examines chromosomal breakage in cells of patients with the heritable disease Fanconi anemia.

Conferring after patient rounds, from left, Martin Carter, Arthur Balin, Alice Gottlieb, Clinical Scholars Andrew Lin and Loretta Pratt, and Nurse-Practitioner Dorothea Caldwell.

her work with a Harlem community health project.

"Inherent in any research," Dr. Carter asserts, "is the possibility—the likelihood—of uncovering information with implications that cross disciplinary boundaries." Zofia Borowska, who has been at Rockefeller for twenty-four years, the last four with Dr. Carter, is a biochemical geneticist who began her career in the laboratory of the late Nobel prizewinning geneticist Edward Tatum. She has conducted a range of investigations stemming primarily from her findings concerning the action of antibiotics on cellular proteins. Most recently, with Dr. Auerbach, she has been applying her knowledge of protein function to the study of Fanconi anemia. This summer she moved from the study of genetic disease to the laboratory of Professor David Mauzerall, who studies photosynthesis and photobiological evolution. "It's not such a strange switch," she explains. "It's all biochemically related."

Alice Gottlieb is an immunologist with an M.D. from Cornell and a Ph.D. from Rockefeller. She was trained in the laboratory of the late Henry G. Kunkel, who led seminal research in autoimmunity, a process in which the body's immune defense system turns on the body itself. Her initial interest was lupus, one of the autoimmune diseases with skin manifestations. Now with Dr. Carter's group, she is studying certain antibodies that have affinities for specific areas of the skin. (Antibodies are the chemical bullets the immune system fires at molecules it perceives as foreign invaders—or misperceives, in autoimmune disease.) She has been developing a battery of monoclonal antibody probes that are helping to characterize the ways in which skin cells respond to various diseases.

James Krueger, another Rockefeller-Cornell M.D.-Ph.D. graduate, started out in virology. He recently finished medical school and is studying pemphigus, also an autoimmune disease. "Before steroid and immunosuppressant therapy," says Dr. Carter, "pemphigus victims uniformly died of its effects. Now they sometimes die from the treatment. Jim is interested in defining the immunologic aberrations expressed in pemphigus, and together he and I have started looking at it as a general model for autoimmune diseases of the skin."

Peter Ross, left, and Postdoctoral Associate Noboru Matsuo in the laboratory where DNA is isolated to learn about how cells repair themselves.

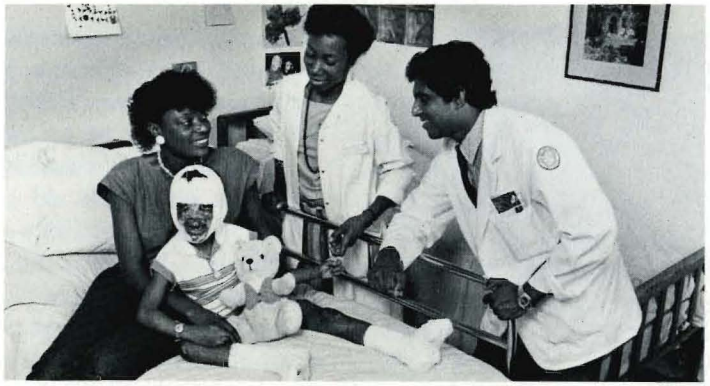
ROOTS AND TENDRILS

Martin Carter had intended a career as a "regular" doctor. There have been physicians in his family for more than a century, mostly in Missouri, where he grew up in the small river town of Doniphan. His entry into research was, he says, a consequence of the Cuban missile crisis.

"I was interning at the time at the University of Rochester and, being newly married, I decided to join the medical officer deferment program of the Public Health Service. I had some background in infectious diseases so I thought maybe they'd send me to Tahiti or someplace like that. They sent me to Philadelphia—with instructions to wipe out syphilis. I didn't quite manage to do that, but I did get to meet a lot of people from the groups that work at Philadelphia General Hospital. One of them was George Hambrick from the University of Pennsylvania, which was then one of the few places where dermatological research was going on. As I got to know George, I realized that dermatology interested me much more than internal medicine."

With Dr. Hambrick's encouragement, Dr. Carter applied and was accepted for a residency in dermatology at the University of Pennsylvania, and from there went to Yale, where in 1970 he became the first Howard Hughes Investigator in dermatology, and where he remained for fourteen years until the invitation came from Rockefeller.

"Moving to New York was a difficult decision," he says. "I



Epidermolyis bullosa patient and his mother receive a visit from Dorothea Caldwell and Mathew Varghese. Dr. Varghese, a pediatrician who recently completed a two-year appointment as a clinical scholar with the Rockefeller laboratory of investigative dermatology, is currently a resident in dermatology at New York Hospital-Cornell Medical Center.

had a very good group in New Haven and we have a lovely, old house in the Connecticut countryside that my family and I get to go to now only on occasional weekends and holidays. But I couldn't resist the opportunity to put together the kind of program I knew could be achieved with the extraordinary resources in and around Rockefeller." One of his first acts on accepting the post was to coax Dr. Hambrick out of semiretirement to become co-chief with him of the dermatology division at Cornell Medical Center.

In their days at the University of Pennsylvania, George Hambrick remembers urging Dr. Carter to become "more than just a clinician." Beyond an obvious talent for research, Dr. Hambrick saw in his young colleague "a born organizer. Marty's a builder, a communicator. Dermatology has suffered from an image problem. People go to dermatologists looking for an easy solution, a quick fix. But solutions don't come without study, and there hasn't been enough in dermatology. Marty has done a lot to raise the level of the science and the image."

If Dr. Carter became more than just a clinician, he has nonetheless remained very much a hands-on doctor, as he describes himself, deeply involved in the day to day care of his patients as well as in the training of a growing number of young cutaneous biologists. Like him, these new clinical researchers spend their days shuttling between the laboratory and the clinic. "The questions I'm interested in answering as a scientist," he says, "arise from the clinical setting. I don't think I'd know what questions to ask without patients."

When patients come to Dr. Carter's clinic at Rockefeller, it's likely the first person they meet will be Dorothea Caldwell. Often, she's the reason they've come in the first place. The boy receiving skin grafts is from Texas. The wounds that are now healing had been reopening for three years. His mother learned about Dr. Carter's work at a meeting of EB parents at which Dorothea Caldwell spoke. A nurse-practitioner with thirteen years of experience and a master's degree in public health, Ms. Caldwell is the clinical coordinator for the laboratory and, as such, bears the major responsibility for enlisting and screening patients, supervising their care in coordination with the laboratory's physicians, and contributing to the research protocols.

"I wasn't sure I'd be interested in dermatology," she says, "but now I don't think I could ever leave. You get so involved with these patients. We usually have about eight inpatients at any one time, and we follow about a hundred outpatients, including some thirty EB families. With EB you find yourself nursing whole families because it's the kind of disease that devastates every member. We try to get to them as early as possible. We have a referral pattern established so that doctors transfer babies from the newborn nurseries directly to us. The younger we begin treatment the better chance we have of preventing the worst effects. Until now, most of these people didn't know where to turn, and there was so little to offer them in the way of help."

The Carter family has put down roots in New York, literally and figuratively. Mrs. Carter, a writer who unwinds by gardening, does her digging these days in Central Park. "She's one of the worker bees there," says her husband, "planting bulbs and hoeing. Our kids—we have three, all grown—think it's very funny when they see her running around picking up litter." Dr. Carter, a passionate music lover, sings with the St. Andrew's Chorale of the Madison Avenue Presbyterian Church, and, according to Dorothea Caldwell, "if you're not an opera buff when you come to this lab you soon become one."

"I figured," Martin Carter says, "if I was going to start something new somewhere I'd rather do it here than anywhere else. For clinical research, Rockefeller is the premier place." □

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