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Eos' Oversight: [Dr. Anthony Cerami]

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*The immortal gods
have neither age nor death;
all other things almighty Time disquiets.*
—SOPHOCLES

THE ROCKEFELLER UNIVERSITY RESEARCH PROFILES

SPRING 1987

Eos' Oversight

When Eos, goddess of the dawn, asked Zeus' permission to marry Tithonus, a mortal, she also requested that he be given eternal life. Unfortunately, she neglected to request eternal youth for him as well. So while she remained an immortal, strong and supple, Tithonus eventually weakened and withered even though his molecular and cellular clock continued to tick. Eos' oversight has significance for scientists seeking to discover the secrets of aging.

Most theories of aging fall into two general categories. The first, and most studied, proposes an accumulation of lethal events within the individual cell, leading to senescence and death. One of the barriers to cellular longevity, called the Hayflick effect, after its discoverer, is the genetic time clock that limits the number of divisions a cell is able to undergo. But even if it were possible to extend cell division indefinitely, physiological function would deteriorate, as Tithonus' did.

Professor Anthony Cerami, who heads The Rockefeller University's laboratory of medical biochemistry, takes another approach. He is investigating the process from the standpoint of age-associated diseases or deterioration. "Our research is concerned not so much with extending the lifespan of an individual as with making old age healthier," he says. For the past twelve years, his laboratory has made remarkable discoveries indicating that many of the functional breakdowns associated with age proceed from a single, fundamental chemical reaction. Conditions such as cataracts and atherosclerosis, to cite two prime examples, result from a commonplace chemical reaction be-

tween the sugar glucose and the proteins that comprise the body's metabolic machinery and structural framework.

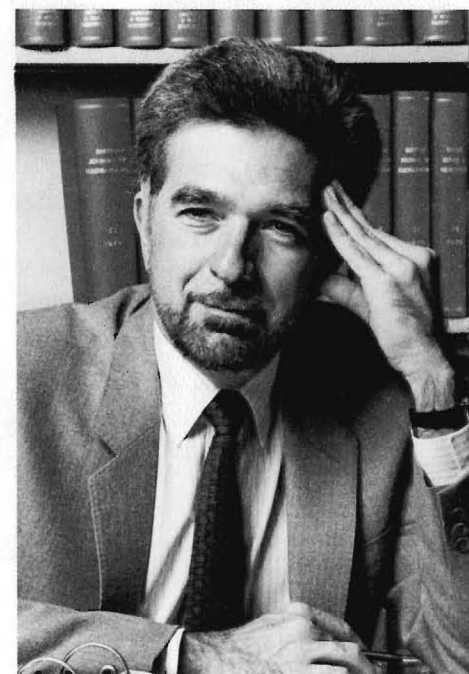
"AGE" AND AGING

Until recently, glucose was generally considered a stable and innocuous molecule serving as a central source for energy. Scientists have since learned that metabolism is not its only activity, and that this abundant and ubiquitous sugar is not always benign.

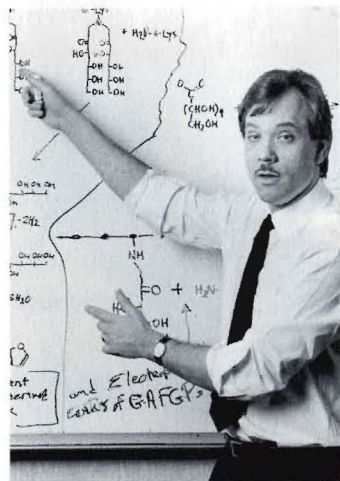
Most biological activities are triggered by chemical catalysts called enzymes. Glucose, however, has the ability to react with proteins and with nucleic acids (the genetic material) through simple proximity, a process called nonenzymatic glycosylation. "A lot of complicated chemistry goes on," says Dr. Cerami, "and if the reaction is permitted to continue, eventually it produces brownish-yellow pigments that can bind two molecules together." Appropriately, Dr. Cerami has named the resulting pigments "AGE,"

for advanced glycosylated end-products. This synthesis of glucose-modified proteins is independent of the amount of sugar we consume. The body can produce glucose from carbohydrates and other foodstuffs, so that the formation of AGE is a continuous, life-long process wherever glucose is permitted to react with proteins.

One familiar manifestation of AGE is the browning of food.



Anthony Cerami



Michael Brownlee, whose experiments have shown that the compound aminoguanidine can prevent hazardous glucose-protein crosslinks.

The skin of a roasted chicken turns brown because the dehydration that occurs during cooking accelerates the formation of AGE. The same reaction turns bread into toast. The effects of AGE over time can be observed simply by comparing dried apricots from a health food store, brown and hard, with the artificially preserved supermarket variety, bright orange and soft. Pathologists have observed that the bones of older people are browner than the bones of youngsters. "Like untreated apricots," says Dr. Cerami, "we're browning all the time."

AGE does more than just discolor tissue. As Dr. Cerami explains, "AGE acts as a chemical glue to attach molecules to one another, forming what we call a cross-link. That is why overcooked meat is so difficult to slice and chew. You are literally sawing through cross-linked proteins with your knife and grind-

ing them down with your teeth." Importantly, these same glucose-derived cross-links have been traced to many physiologic manifestations of old age.

Since the formation of AGE occurs during the later stages of nonenzymatic glycosylation, the proteins involved must be long lived. Many of the crystallin proteins in eye lens remain intact our whole lives. Dr. Cerami's experiments have shown that cataracts can result from cross-linked proteins accumulating in the lens, preventing light from passing to the retina. His research has also demonstrated that cross-linked proteins can form in the tissue of the lungs, heart, and arteries, contributing to their progressive inelasticity. Glucose can react to form cross-links with collagen, the major protein in skin and connective tissue.

Another manifestation of aging is the impairment of DNA function. In addition to transmitting our inheritance from generation to generation, DNA, deoxyribonucleic acid, encodes the instructions that cells need to make proteins. Based on recently published work, Dr. Cerami and former bio-medical fellow Richard S. Bucala believe that AGE may be involved in the chromosomal aberrations and breakage in DNA molecules characteristic of old cells.

THE POWER OF CHEMISTRY

Oddly enough, chickens brought Dr. Cerami to the exploration of science. When he was a boy growing up on a farm in New Jersey, a chicken infection called coccidiosis would regularly wipe out half of his family's flock. In the 1950s, a new drug was introduced against the disease. "It seemed miraculous," he recalls. "We would give the drug to the chickens and they didn't die. I thought it would be wonderful to be able to use chemistry as a way of doing something as meaningful as that."

At Rutgers University's College of Agriculture he learned about basic chemistry and animal husbandry. His training as a research scientist began at The Rockefeller University, where he studied nucleic acid chemistry with Professor Edward Reich in the laboratory of Nobel Laureate Edward Tatum. After receiving his Ph.D. in 1967, he spent some time at Harvard Medical School learning the medical application of biochemistry. In 1969, he was invited to return to Rockefeller, where he has remained.



Glucose binds to proteins in arterial wall (A), rearranges itself (B), and binds to other protein strands (C) or to cholesterol-bearing low-density lipoproteins (D). Aminoguanidine inhibits cross-linking (E) and thus may prevent the hardening and narrowing of arteries that occur in diabetes and aging.

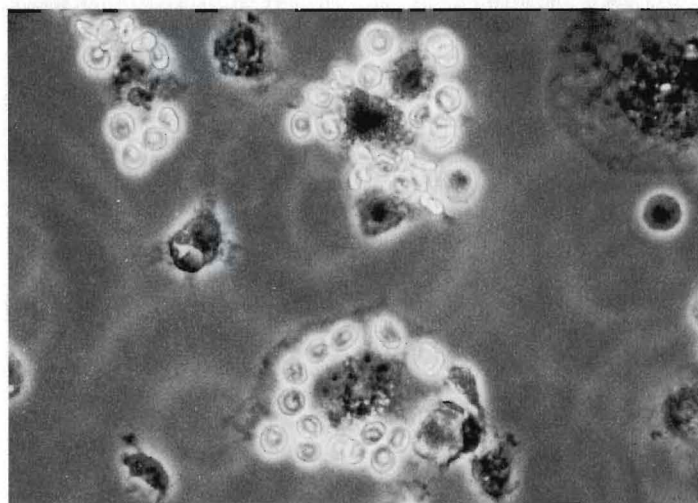
Dr. Cerami's first clue to the far-reaching effects of nonenzymatic glycosylation came from work he was doing in the 1970s on the blood disease sickle cell anemia. The disease is so named because the red blood cells of its victims become sickle-shaped in the absence of oxygen instead of remaining oval. These sickled cells can block blood vessels and starve tissues of oxygen. Previous experiments elsewhere had reported that urea, a compound excreted by the kidneys, prevents sickling. But urea seemed to Dr. Cerami an unlikely therapy since the amounts needed would be unsafe.

Dr. Cerami remembered as a graduate student attending a lecture by Stanford Moore, one of the Rockefeller's pioneer protein chemists. In the lecture, Dr. Moore discussed the active properties of the small amounts of cyanate normally found in urea solutions. The recollection suggested a course of experimental inquiry. And, in fact, Dr. Cerami and Professor James Manning, a Rockefeller colleague, did find that cyanate could prevent sickling. However, it was still not sufficiently safe. Patients given the compound began to form cataracts and to lose the protective myelin sheath around peripheral nerves in the legs, a condition called peripheral neuropathy. While the side effects ruled out cyanate as a treatment for sickle cell disease, they provided a springboard to a new area of research.

Both cataracts and peripheral neuropathy are frequent complications of diabetes. Dr. Cerami wondered why diabetics displayed the same problems as sickle cell patients treated with cyanate. His hunch was that "in diabetes there was something like cyanate reacting with the hemoglobin in the blood, which was also reacting with the lens crystallins in the eye and the nerves of the leg." That something turned out to be glucose.

From previous work in the laboratory of Helen Ranney at Albert Einstein College of Medicine, Dr. Cerami knew that a type of hemoglobin, called hemoglobin A_{1c}, is elevated in diabetic patients. Further research by Dr. Cerami and his colleague Ronald J. Koenig revealed that hemoglobin A_{1c} is a modification of hemoglobin resulting from chemical interaction with glucose, and that the more glucose present in the patient, the more rapidly hemoglobin A_{1c} was made.

This led to the realization that the measurement of hemoglobin A_{1c} could not only identify the presence of diabetes but could also provide an accurate measurement of the average



Glucose-modified red blood cells surrounded and ingested by macrophages.

glucose concentration in the blood over the course of a month. Today, this finding is applied by physicians throughout the world to assist in the diagnosis and management of diabetic patients. On an investigative level, the observation of how glucose reacts with long-lived proteins like hemoglobin provided a new perspective for studying how our bodies age.

Just as diabetes provided a clue that glucose and proteins formed AGE pigments, the chemical structure of the AGE has since provided a clue to a new treatment for the complications of diabetes. The rate of AGE synthesis is dependent both on time and on the amount of glucose in the blood. Because the blood glucose concentration is greater in diabetics than in normal people, they exhibit AGE-related diseases earlier, particularly cataracts and vascular problems. Biochemically, diabetics age more quickly than non-diabetics.

Proteins in the blood vessel wall can undergo a chemical rearrangement with glucose to form molecular traps. These traps can snare proteins floating by in the blood. The attached proteins can collect in the vessels and block the free flow of blood. Among the proteins that become stuck is the cholesterol-containing LDL, or low-density lipoprotein, a major contributor to atherosclerosis and heart disease. Dr. Cerami reasoned that if a drug could be found to block the AGE traps, the plasma proteins would be deprived of anchoring sites and



Current research by Helen Vlassara focusses on the role of white cells called macrophages in the removal of aging proteins.



Dr. Cerami with laboratory colleague Mary R. Rifkin, right, and graduate student Annette Lee. In addition to their research posts, Dr. Cerami serves as dean of graduate and postgraduate studies and Dr. Rifkin as an associate dean.

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the artery-clogging process interrupted.

For years, food chemists have treated fruits and other foods with sulfur dioxide to prevent browning. Michael Brownlee, of the Cerami laboratory, tried sulfur dioxide with proteins incubated with glucose. While it prevented discoloration, it did not prevent cross-linking. The search widened to other chemicals. Peter Ulrich, who was working on the chemical structure of AGE, joined forces with Dr. Brownlee in identifying the compound aminoguanidine. This has proven, at least in animal trials, to be capable of preventing the formation of AGE cross-links and the adhesion of plasma proteins to the vessel walls. Further research is needed before the drug can be used clinically, but its potential for inhibiting vascular complications, says Dr. Brownlee, "is an exciting possibility we'll be exploring over the next few years."

Not all proteins with AGE are fated to survive. When glucose and protein are placed together in the test tube, many more cross-links are formed than occur in nature. Clearly, the body has its own mechanism for the recognition and removal of AGE molecules. If this mechanism could be identified and harnessed, age-associated disease might be slowed or stopped naturally without the introduction of cross-link-inhibiting drugs.

A clue to the body's mechanism for protein removal was found by Helen Vlassara while she was studying the removal of the myelin sheath of peripheral nerves of diabetics. Having shown that glucose reacts with the myelin protein to form AGE, Dr. Vlassara noticed that macrophages could specifically take up these modified proteins. Macrophages are white blood cells that can act as the immune system's scavengers. She has since demonstrated that highly-specific receptors on the macrophage cell surface selectively "recognize" senescent proteins that need to be disposed of. "Unfortunately, as we become older, macrophages become less efficient and tend to leave behind a certain amount of AGE, which accumulates over time," Dr. Vlassara explains. She is currently studying the AGE receptor on the macrophage and developing strategies to speed up the removal of targeted cross-linked proteins.

PARADOXES

In addition to investigating the diseases of aging, Dr. Cerami's laboratory has been studying the wasting of the body that occurs in animals or people with parasitic diseases or tumors. Conventional medical wisdom decreed that this wasting

phenomenon was a result of parasites or tumors feeding off their hosts' energy. But when Dr. Cerami examined samples of blood from cows and rabbits infected with trypanosomes, the agents of African sleeping sickness, he found the number of parasites surprisingly low. It did not seem possible that so few assailants were causing such extreme emaciation and lethargy, a condition called cachexia (pronounced ka-KEX-ee-ah). Further investigation revealed a further paradox. The blood of the animals was rich in fat. "We were faced with a situation," Dr. Cerami says, "that required of us to ask, 'what's going on here?'"

Crucial to the body's proper utilization of fats is the enzyme lipoprotein lipase. Without it, complex fatty substances circulating in the blood cannot be metabolized and stored as energy in cells. From blood samples of cachectic animals, Masanoba Kawakami of the laboratory was able to identify a molecule that prevented the synthesis of the enzyme. This suggested that the molecule's role may be the mobilization of energy for quick response against invading microorganisms. When infection becomes chronic, however, the continuing presence of the molecule, which they dubbed cachectin, becomes a fatally damaging factor.

Cachectin appears to cause cachexia in patients infected with bacteria as well as in those with parasitic disease. The laboratory's research also indicates that cachectin may be one of the body's major mediators of the fatal condition associated with infection called septic shock.

But the big surprise was still to come. When cachectin's molecular composition was identified by Bruce Beutler, who has recently moved to the Howard Hughes Medical Institute in Dallas, it was found to be identical to tumor necrosis factor, or TNF, a compound that is being evaluated as a drug against cancer. Discovered at Memorial Sloan-Kettering Cancer Center, TNF has the ability to kill certain tumor cells. To what extent the discovery of its cachexia and shock-inducing properties will make it necessary to modify its use in cancer therapy is a question under intensive investigation.

Substances like glucose and cachectin that play more than one biologic role are recurring themes in Dr. Cerami's research. They are proving to be pivotal elements in explaining extremely complex phenomena. "It is my hope," says Dr. Cerami, "that our studies will provide new insight into some of the medical questions that have intrigued mankind since earliest times."

