This white substance, a multiple-target drug, saves mice from certain death—and may prolong human life

SUPERPOWDER

BY ALBERT ROSENFELD

The black mice in two cages, side by side, stir up memories of ancient fables. Those in one cage are sleek and healthy. Those in the other appear fatter and older. Yet all the mice are the same age and the same breed, like siblings in a venerable morality tale about the rewards of good living and the wages of dissoluteness.

In fact, the story of these mice is more dramatic than a fable. Both sets of mice at Temple University's Fels Research Institute, in Philadelphia, are in potentially grave danger. All have inherited susceptibility to a serious disease that causes their antibodies, meant to attack invading microorganisms, to kill their own blood cells instead. The fatter mice are developing anemia as a result of this genetic affliction. Chances are, they will die from it. The slim and healthy animals are protected by a white, powdery sub-

PHOTOGRAPH BY ANTHONY WOLFF

stance sprinkled liberally on their food. The substance, a hormone called DHEA, is prolonging their lives.

Medical researchers since Hippocrates have sought the magic bullet to cure all ills. No one is claiming that DHEA is it. But early returns from research suggest that this natural hormone whose full name is dehydroepiandrosterone, may be able to hit multiple targets with a single shot.

Biochemist Arthur G. Schwartz, master of the Temple mice, points out that DHEA seems to counter obesity as well as to protect the lab animals from their genetic disease. The slender, scholarly scientist (shown, with one of his mice, in the photo on the previous page) is not given to overstatement. But Schwartz says the hormone might very well work on humans too. DHEA could also help combat diabetes, prevent cancer, and safeguard the cardiovascular system from heart attack or stroke, Schwartz says. It might even provide a first-line defense against aging.

Consider just one effect of DHEA. It inhibits the production or function of an enzyme called G-6-PD (glucose-6-phosphate dehydrogenase), which is essential to the body's use of sugar. Any substance that can interfere with this metabolic "pathway" is bound to affect a number of the body's important functions, including cell division. It is not at all amazing that a G-6-PD inhibitor would have varied uses. Besides, DHEA influences other biochemical pathways that relate to such vital processes as fatty-acid metabolism and the making of DNA, the molecular basis of heredity. So versatility is built right into it.

The relative obscurity of DHEA outside the scientific community may seem strange in view of its abundance in our bodies. For example, it is something like 20 times as plentiful in our blood as the hormone cortisone—which, like DHEA, is made by the adrenal glands, two inch-wide glands, one atop each kidney. And the population of DHEA molecules in the circulation on a given day may outnumber a thousandfold those of the sex hormones. Yet though most of us are familiar with all those estrogens and androgens, despite their sparsity, few of us have ever heard of DHEA.

The main problem has been to define DHEA's primary biological role. "For a long time there was reluctance even to recognize it as a hormone. You still won't find unanimity on that score among endocrinologists," Schwartz says.

DHEA does not act like most hormones and is, in fact, hard to find stored in the adrenals themselves. It seems to be released into the bloodstream as soon as it is manufactured. Another source of confusion is that DHEA can act as a precursor (forerunner) of the sex hormones. Yet that could scarcely be its main purpose. Why would so much of it be needed to make such tiny quantities of estrogens and androgens? DHEA can also be a metabolite, a leftover product of other hormonal reactions, and some have speculated that DHEA is merely a "waste steroid," a useless by-product bound for excretion.

Indeed, DHEA is excreted in quantity. Nevertheless, researchers have found it in the testis, the ovary, the placenta, the fetus, and the lungs. And now the pioneering French investigator Etienne-Emile Baulieu of the University of Paris has extracted DHEA from the brains of rodents and primates—where he believes it is produced locally rather than imported from the adrenals. DHEA, he believes, can thus hardly be thought of as a mere waste product.

Rather, says biochemist Norman Applezweig, who runs his own New York consulting firm, "DHEA must have a role in the living system, one that has thus far eluded us." He suspects that DHEA will prove to be nothing less than a "regulator of metabolism in health and disease." As he points out, DHEA has already been tried as therapy—mostly in Europe—for a variety of human diseases, among them psoriasis, osteoporosis (a disease in which bones lose their calcium), gout, depression, hypertension, diabetes, and the disorders of menopause. But the results were questioned and in almost every case were attributed to the conversion of DHEA, somewhere in the body, to male or female hormones. With new approaches to testing, and new understanding of DHEA's mechanisms, however, Applezweig is convinced that it may well become the most important drug of its kind ever to be developed.

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Most of the studies in this country have been carried out, so far, in animals. But clinicians who know of DHEA's potential—especially in breast cancer, obesity and diabetes—are itching to start human tests.

Spearheading the new investigative thrust is Arthur Schwartz's group at Temple. Like many research scientists, Schwartz was initially attracted by the mysteries surrounding DHEA. Why should the adrenals secrete the substance in such generous quantities? He was especially fascinated by studies carried out in the 1950s indicating that DHEA production reaches its peak at the age of about twenty-five, then declines steadily. Research by Claude Migeon at Johns Hopkins, by birth-control-pill pioneer Gregory Pincus, and by a team of investigators in Japan shows that toward the end of life, DHEA levels have diminished to 5 percent of these peak values. Such a dramatic, steady decline is unheard-of among such hormones. Why does DHEA decline?

There were other curious pieces to the puzzle. Schwartz was drawn to a series of articles that appeared in the 1970s, mostly in British medical journals, reporting the results of a still-ongoing investigation of breast cancer in women by scientists at London's Imperial Cancer Research Fund. What particularly caught Schwartz's eye in these studies headed by cancer specialist Richard D. Bulbrook was the fact that DHEA was consistently below normal in women with breast cancer as well as in women who were predestined to develop breast cancer.

One never knows, in studying cancer, what is cause and what is effect. People with cancer lack normal levels of immune protection, for instance, and this might simply be one of the side effects of the disease. But a growing number of researchers believe that an impaired immune system is one of the preconditions permitting cancer to develop. Could the same be true of DHEA? If its absence or scarcity invariably accompanies breast cancer, might its presence be protective or even therapeutic?

In the early 1970s Schwartz happened to be working with rat-liver cells in tissue culture. In this environment the cells are easily rendered malignant by dosing them with cancer-causing chemicals. He was looking for ways to prevent this transformation by protecting the cells with various steroid substances, members of a class of organic compounds including various hormones. Why did Schwartz focus on steroids? Well, Schwartz explains, "carcinogenic chemicals often look like steroids, structurally speaking. And in biochemistry there is a well-known phenomenon called competitive inhibition. Molecule A may cause a certain reaction. Molecule B, if it is sufficiently similar, will compete successfully, even preferentially, to react before A does. Thus, A will be inhibited from carrying out its intentions. For this reason, drug companies often look for a substance that is similar in structure. And that was my idea—to find a similar steroid that would competitively inhibit the carcinogen and leave the cells normal.

So when I saw Bulbrook's paper connecting DHEA with breast-cancer inhibition, I quickly got hold of some DHEA—for the wrong reason, as I now know. DHEA works not by competitive inhibition but by blocking G-6-PD [the enzyme that regulates sugar metabolism]. Nevertheless, it did work. With DHEA in the culture, the cells were protected. They didn't turn cancerous.

Schwartz soon moved from tissue cultures to animal cancer studies of his own.

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