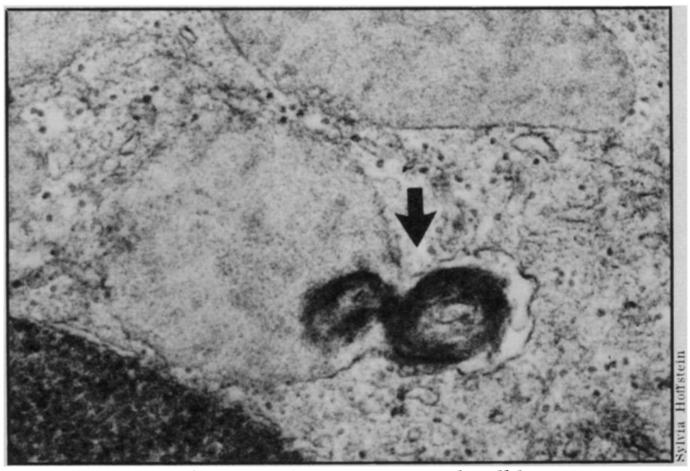
Correcting Enzyme Defects In the Test Tube



Enzyme in liposome fuses (arrow) with cell lysosome.

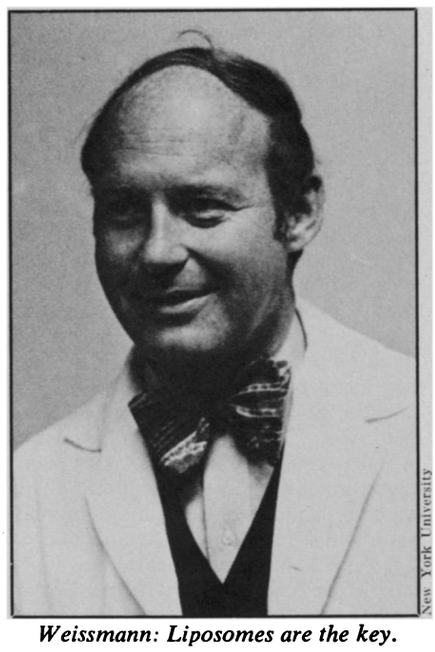
Enzyme engineering looms as therapy for persons suffering from certain fat and sugar metabolism diseases

by Joan Arehart-Treichel

Traditionally, physicians have been able to do pathetically little to help persons with enzyme deficiencies that lead to an excess accumulation of fats or sugars in the body. The aberrant buildup of fats or sugars can gravely damage tissues and organs. It often paves the way to a tragically premature death.

During the past two years, however, definitive help for these persons has emerged from the biochemistry laboratory, in the form of enzyme therapy. And even more therapeutic assistance for these people should be at hand in the near future, in the form of enzyme engineering in the test tube. The enzyme-engineering technique that looks promising, in fact, may also benefit patients with rheumatoid arthritis and gout—two diseases that constitute enzyme leaks rather than enzyme deficiencies.

In the past, investigators envisioned helping patients with enzyme-based fat and sugar metabolism diseases by giving them enzyme injections. In other words, patients would receive normal versions of those enzymes that they lack. When the investigators attempted to apply the concept, however, they could not sufficiently purify the needed enzymes or get the enzymes to those areas of patients' bodies where they were desperately needed. Finally Roscoe O. Brady and his colleagues at the National Institute of Neurological Diseases and Stroke managed to do so, for two patients with Fabry's disease and for two patients with Gaucher's disease (SN: 11/23/74, p. 327). Both diseases result in excess accumulation of fats due to a faulty fat-metabolism enzyme. The enzyme injections improved the patients' conditions considerably.



Weissmann: Liposomes are the key.

Now Gerald Weissmann of the New York University School of Medicine and his colleagues are taking another tack toward treating patients. Some have Gaucher's disease or Fabry's disease, others have other enzyme-based sugar and fat metabolism ailments—Tay-Sachs disease, Niemann-Pick disease, Pompe's disease, the Hunter-Hurler syndrome. Their strategy consists of incorporating normal enzymes, which patients lack, into artificial organelles called liposomes, then injecting the enzyme-laden liposomes into the patients. "It's generally a way of doing intracellular engineering," Weissmann explains.

The one thing that unites these diseases is that they involve defects in lysosomal enzymes. Lysosomes are tiny

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membrane-bound sacs in the cytoplasm of cells. They engulf foreign matter. The matter is then shredded, garbage-disposal style, by enzymes in the lysosomes. So Weissmann and his colleagues started plotting ways they might replace the lysosomal enzymes that are missing or inactive in patients with these diseases.

Several years ago, they found that one lysosomal enzyme—a so-called peroxidase—could be captured in liquid solution in a package called a liposome. Actually the liposome is made of membranes similar in composition to those that surround the cell and the lysosome itself. In the liposome, the membranes are organized in tight, globular masses many layers thick. The enzyme is trapped in water-filled spaces between the layers.

At that time, they theorized that liposomes might serve as vehicles for the introduction of normal lysosomal enzymes into cells with genetically deficient lysosomal enzymes. They found, however, that their liposomal-coated peroxidase could not gain entry through the cell membrane, nor in turn through the lysosomal membrane. They reasoned, however, that a cell membrane, and in turn a lysosomal membrane, might be tricked into letting the liposomal-coated peroxidase through if the liposome were first coated with antibodies.

Their rationale was that the cell, and in turn the lysosome, would regard the antibodies as foreign particles—matter to be ingested and done away with. They tried coating the liposome-peroxidase package with antibodies first. As they hoped, the cell membrane and in turn the lysosomal membrane, let the antibody-liposome-peroxidase package through. Thus the peroxidase gained access to a cell's lysosome and was able to function as a normal enzyme.

Using this sneak-through ploy, they managed a 50 percent success rate in getting all the peroxide enzymes into cells' lysosomes. In contrast, when they added free peroxidase enzymes to cells, a mere one percent of the enzymes penetrated the cells' lysosomes. So it looked as if the sneak-through approach was indeed superior. They reported these encouraging results in the January PROCEEDINGS OF THE NATIONAL ACADEMY of SCIENCES and forecast that their technique might well offer a means of getting many different kinds of lysosomal enzymes into cells that are deficient in them.

Since then, Weissmann and his team have come even closer to fulfilling their ultimate ambition—correcting human lysosomal defects by test-tube engineering. With Satish Srivastava of the University of Texas, they have purified a normal lysosomal enzyme called hexosaminidase A. This is the enzme deficient in patients with Tay-Sachs disease. Using the antibody-coated liposomes as carriers, they have managed to introduce the normal enzyme into the cells of four patients with Tay-Sachs disease, and the enzyme functions normally in these cells. What now remains is to successfully inject the liposome packages into patients and to make sure that the cells containing the normal functioning enzymes home their ways to areas of the body that need them. Weissmann is convinced that such strategy will work. But first he will inject the liposome packages into lab animals to make sure.

The New York City rheumatologist anticipates the day where patients with either Tay-Sachs disease or with one of the other 30 or so lysosomal enzyme deficiency diseases will receive liposome-packaged enzymes as regular therapy. "Patients with these diseases," as he sees it, "have a sort of sugar or fat constipation. They get chock-full of these compounds and can't get rid of them. If we can give them normal sugar and fat metabolizing enzymes every couple of weeks, the enzymes should purge them of their abnormal complex sugars or fats."

For rheumatoid arthritis and gout patients, enzyme engineering would work somewhat differently, Weissmann anticipates. The reason is that rheumatoid arthritis and gout involve leakage of lysosomal enzymes (causing joint inflammation), rather than defects of lysosomal enzymes.

Weissmann envisages an elegant rubric. A chemical compound that inhibits lysosomal enzymes would be packaged in liposomes. The liposomes would be incorporated in cells. The cells would be injected in a patient. The liposomes in the injected cells would migrate into the lysosomes of the inflamed cells and release the chemical inhibitor. The inhibitor would stop the lysosomal enzyme leaks. "Thus nasty lysosomal enzymes," Weissmann says, "would be inhibited and would no longer cause inflammation."

But why not sidestep this complex strategy and simply inject the chemical inhibitor into a patient? "Our approach should get more of the chemical inhibitor into needy tissues," Weissmann answers. Still, he admits that the approach is still on the drawingboard. For now, he and his colleagues are concentrating on bringing the enzyme-engineering technique to the point where it can help patients with fat and sugar metabolism diseases.

Weissmann and his co-workers will report their progress toward this goal at the annual meeting of the Federation of American Societies for Experimental Biology in April and at the annual meeting of the Association of American Physicians in May. □