

The Return of Thalidomide

A shunned compound makes a scientific comeback

By TINA ADLER

Thalidomide, widely prescribed in the 1950s to alleviate morning sickness during pregnancy, became the lead character in a horror story several years after it came on the European market. In 1961, scientists discovered that the popular pill, also used as a sedative, stunted the growth of fetal limbs. Thousands of children, most of them German, suffered deformities because of the drug. Taking even one dose fairly early in a pregnancy, when limb buds are forming, puts the fetus at risk, scientists believe.

But get ready for a surprise sequel. According to researchers experimenting with the compound, thalidomide may star in an upbeat tale of modern medicine.

Thalidomide has never been okayed for use in the United States except for experimental purposes. The Food and Drug Administration withheld its stamp of approval because the drug can cause peripheral neuropathy, a tingling and numbness in the toes and fingers. Since the 1960s, physicians have used the drug primarily for treating leprosy patients outside the United States.

Other than its danger to the fetus, however, the product appears to pose no significant health risks, researchers say. In fact, physicians prescribed the drug so readily in the 1950s in part because people could not easily overdose on it. As strange as it may seem to anyone who lived through the thalidomide-baby era, the drug's popularity among scientists stems in part from its safety record.

But it is the recent discoveries about how thalidomide works that have piqued many researchers' interest in the compound.

"Thalidomide is being reborn as an immune-modulating agent," says Jeffrey M. Jacobson of the Bronx Veterans Affairs Medical Center and Mt. Sinai School of Medicine in New York. The drug inhibits production of tumor necrosis factor alpha (TNF- α) by white blood cells called monocytes, scientists at Rockefeller University in New York and their colleagues reported in 1991.

TNF- α wears both a white and a black hat. It helps fight infections and malignant

cells. But elevated concentrations of the protein in the blood are associated with the fever, weight loss, and general debilitation suffered by people with cancer, tuberculosis, and AIDS, scientists have found. Moreover, TNF- α helps boost replication of HIV, the AIDS virus, they suggest.

Last year, scientists demonstrated that thalidomide's effect on TNF- α may benefit individuals infected with HIV. The drug inhibited production of the virus in the peripheral mononuclear immune cells of 16 out of 17 patients with AIDS, Rockefeller's Sanit Makonkawkeyoon and his colleagues reported in the July 1, 1993 *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (PNAS)*.

This finding tantalizes researchers, although they have yet to replicate it or determine its clinical significance, Jacobson notes. The drug may well have other effects on the immune system that need exploring, he adds.

Recent studies suggest that thalidomide also slows production of TNF- α without suppressing patients' immune systems, researchers report.

Robert J. D'Amato and his colleagues at Harvard Medical School in Boston announced another important discovery recently: Thalidomide thwarts angiogenesis, the growth of new blood vessels, which is crucial to fetal limb development. In the April 26 *PNAS*, D'Amato and his colleagues reported their attempts to measure this inhibitory effect in rabbit corneas. Thalidomide's ability to inhibit angiogenesis appears unrelated to its effects on the immune system, they assert. The product also stops menstruation, additional evidence of its antiangiogenic abilities, D'Amato adds.

How the drug inhibits angiogenesis remains unclear. But this feature may make the compound useful in the treatment of pathological angiogenesis related to tumor growth and to two eye disorders, diabetic retinopathy and macular degeneration, they speculate.

Researchers have eagerly taken hold of these new speculations and data about thalidomide and have begun using the drug to experimentally

treat patients with AIDS, cancer, rheumatoid arthritis, tuberculosis, and macular degeneration. Recipients of bone marrow transplants may also benefit from the drug, scientists speculate.

The National Cancer Institute in Bethesda, Md., plans to support five trials of thalidomide for patients with advanced Kaposi's sarcoma, melanoma, brain tumor, breast cancer, or prostate cancer. By inhibiting angiogenesis, thalidomide may thwart tumor growth, if not actually shrink tumors, and prolong patients' lives, says NCI senior investigator James M. Pluda.

The studies will evaluate the effectiveness of the drug at slowing disease progression in some 150 to 180 patients and should begin this winter or early next spring. Female participants in the research will be warned of thalidomide's potential to cause birth defects, Pluda notes. These women must have a pregnancy test before entering the study, use birth control or abstain from sexual intercourse during the trial, and leave the study if they become pregnant, among other safeguards.

Early next year, Stuart Fine at the Scheie Eye Institute in Philadelphia, D'Amato, and their colleagues will begin the first test of the drug's effectiveness in treating age-related macular degeneration, a leading cause of blindness in people over 64. The disease results when blood vessels grow and bleed in the macula, a part of the light-sensing retina. The study should prove whether or not the drug inhibits the creation of new vessels in the human eye, D'Amato contends.

Researchers at Rockefeller and elsewhere are following up on the connection between TNF- α and thalidomide. The Rockefeller investigators want to determine how thalidomide influences the weight loss associated with AIDS and to monitor the amount of HIV present in patients' blood and cells — their viral burden. Increases in viral burden correlate roughly with progression of AIDS.

In one study, the researchers gave thalidomide or a placebo for 3 weeks to

41 male AIDS patients who had lost weight for the last 6 months, they reported in August at the Tenth International AIDS Conference in Japan. Half of the group that received the drug also had tuberculosis. Participants taking thalidomide increased their weight by an average of 4.5 percent; the others achieved only a 0.9 percent gain.

The scientists did not find any clear evidence that the compound alters viral burden, says Patrick Haslett of Rockefeller. They did, however, find a correlation between HIV and TNF- α concentrations, he says.

Measuring concentrations of TNF- α is not an exact science, researchers point out. For one thing, the body produces different amounts of it at different times, says Haslett. For another, scientists disagree about whether to measure all TNF- α or only a particular form of it, he says.

The group plans to recruit 93 AIDS patients for a new study designed to examine thalidomide's safety, how well people tolerate the drug, and its effect on weight gain and viral replication. Other researchers have also reported that the compound helps boost AIDS patients' appetite and weight.

The infamous drug also appears useful in treating aphthous ulcers, which form in the mouth and esophagus of some AIDS patients. Jacobson currently oversees a multicenter trial designed to evaluate thalidomide's effects in 168 people with these ulcers and to determine whether the drug alters the volunteers' viral burden.

For years, researchers have investigated thalidomide's effectiveness in treating patients who receive bone marrow transplants and develop the potentially fatal graft-versus-host disease (GVHD) (SN: 3/28/87, p.198). The illness can cause diarrhea, difficulty moving, blindness, mouth ulcers, and other symptoms.

The results "look encouraging... but it's way too early to know," says Georgia B. Vogelsang of Johns Hopkins University School of Medicine in Baltimore.

GVHD occurs in part because of an overload of immune cells. Before undergoing surgery, transplant patients receive drugs and radiation treatment that almost destroy their immune function. This causes them to develop infections. What's left of their bodies' immune systems pumps out a lot of cytokines, including TNF- α , to fight the invaders, Vogelsang says. In addition, the new marrow sends out an army of immune cells that attacks the recipient's gut, liver, and skin, she says. Thalidomide appears to help by stemming this flood of immune cells, she asserts.

Vogelsang and her colleagues found in a 1992 study that after 18 to 24 months of treatment with thalidomide, 28 of 44 GVHD patients survived, including 10 of

the 21 at high risk of dying. Normally, only 20 percent of the high-risk patients would be alive after 6 years. Of the 28, 14 had complete recoveries; the others recovered partially. The only side effects the volunteers experienced were sleepiness and constipation.

Part of the treatment included giving the participants cyclosporine, an immunosuppressant that boosts the effect of thalidomide, Vogelsang says. Her group reports its findings in the April 16, 1992 *NEW ENGLAND JOURNAL OF MEDICINE*.

The researchers have begun a new trial with 18 GVHD patients to test the 1992 findings. Preliminary results look similar, says Vogelsang. In this study, they also reduce the number of lymphocytes, a kind of immune cell, by exposing participants to ultraviolet light, which kills these cells through the skin.

And like others, Vogelsang's team is looking into more than one possible use for thalidomide. Animal studies conducted by the group suggest that the compound may help heart transplant patients.

Researchers at a number of universities are testing the drug in three diseases that involve the overproduction of TNF- α — asbestosis, caused by the inhalation of asbestos, Crohn's disease, and inflammatory bowel disease. Andrulis Pharmaceuticals Corp. in Beltsville, Md., one of the few U.S. manufacturers of thalidomide, is collaborating on these trials, as well as on Jacobson's multicenter study, says company president Peter Andrulis. His company and the University of California, Los Angeles, may begin a study next year of thalidomide's potential benefit for multiple sclerosis patients, he says.

Scientists now consider thalidomide potentially quite useful, despite its ugly history. But they also understand its dangers. People are much more sensitive to the drug than rats, which helps explain how the product slipped by regulators in other countries.

In most cases today, researchers do not conduct animal tests before giving the drug to people, Pluda and other scientists acknowledge. For one thing, researchers haven't developed animal models for cancer or HIV-related diseases in which to test the drug, Pluda says. For another, the compound has a long history of safety, with the obvious exception of the thalidomide-baby experience of the 1950s.

"If we didn't have 35 years of toxicity data, we wouldn't be [comfortable con-

ducting these human studies]," Pluda explains. Researchers are testing other angiogenesis inhibitors as well, but only thalidomide is ready for human efficacy trials, he adds.

Some investigators take strong precautions to protect their female volunteers. Jacobson's team, for example, requires women to use both a barrier and a hormonal method of birth control and to get weekly pregnancy tests. Before entering the study, they must read a detailed consent form and answer questions about what they read, he says. Companies that manufacture the drug must take extra care to prevent their female employees from being exposed to the compound, researchers point out.



Chemist Mary Shire of Celgene Corp. in Warren, N.J., experiments in the laboratory with producing drugs that mimic thalidomide. Celgene, which provides thalidomide to researchers, has companies outside the United States formulate its thalidomide recipe.

No one knows how the public and the medical community would respond to seeing thalidomide on pharmacy shelves. Certainly, some people would protest its arrival, scientists acknowledge. But many investigators are adamant about the value of exploring the drug's potential benefits.

Many doctors have strong — and unfair — prejudices against the compound, says Kenneth I. Kaitin of the Center for the Study of Drug Development at Tufts University in Boston. "The fear of birth defects associated with the drug... is the worst reason for not pursuing new uses for it," he argues. Particularly for treating HIV-infected patients, "it absolutely should definitely be followed up. The evidence that it could be effective is very compelling."

Other drugs already on the market pose a threat to the fetus, and scientists know less about their toxicity than about thalidomide's dangers, Pluda adds.

Still, images of thalidomide babies fade only slowly from memory. "We're all wrestling with the history of thalidomide and its potential for doing harm," says Jacobson. □