

Release of Study Ends Drug Fracas

The plot has all the twists of a pulp thriller, with a cast of dedicated scientists, private investigators, and profit-minded corporate executives out to protect their stake in a lucrative, life-saving drug. What's more, it's true.

Now, 9 years after this scientific imbroglia began, the scientists' conclusions and the company's acknowledgment of its efforts to quash the research appear in the April 16 *JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (JAMA)*.

Central to the story is an experiment involving the drug Synthroid, a synthetic hormone used to treat thyroid disease. In a study of just 24 patients, Betty J. Dong of the University of California, San Francisco (UCSF) and her colleagues found in 1990 that Synthroid and three cheaper drugs are equally effective.

They also learned a lesson about the pitfalls of corporate funding of university-based research. The study was initiated by Flint Laboratories in 1987 to prove that Synthroid was superior to other thyroid drugs. Flint, knowing Dong had previously reported favorable findings

about Synthroid, selected her team, paid \$250,000 to finance the researchers' work; and signed them to a contract that barred them from publishing results without permission.

Flint was bought by Boots Pharmaceuticals of Lincolnshire, Ill. Boots then merged with Knoll Pharmaceutical Co. of Parsippany, N.J. Boots had become suspicious that the investigators were leaking information to rivals, says Knoll spokeswoman Linda Mayer. Although the company hired private investigators, they found no evidence to support these suspicions.

Both Boots and Knoll did everything in their power—from mounting a disinformation campaign to flexing their legal muscles—to keep the researchers from publishing their conclusions.

Now at stake is Synthroid's 38-year dominance of the \$600 million U.S. thyroid supplement market. Each year, doctors write 15 million prescriptions for hypothyroidism. Eight million of these are for Synthroid, says Knoll spokeswoman Linda Mayer. Without treatment,

this metabolic disease can cause lethargy, stiffness, forgetfulness, madness, coma, and even death.

Drug therapy involves replacing the missing thyroid hormone with levothyroxine. Natural thyroid hormone was used until Synthroid, the first synthetic version of the hormone, was introduced in 1958. Because thyroid hormone had been used safely for decades and because Synthroid is virtually identical to it, Synthroid was exempt from Food and Drug Administration (FDA) regulation. No newer versions have matched Synthroid's sales.

In a carefully controlled study that withstood the scrutiny of UCSF and JAMA reviewers, Dong and her colleagues placed the 24 patients on a rotating schedule of Synthroid, two generics, and Levoxyl, made by Jones Medical Industries of St. Louis, Mo. Cheaper substitutes were as effective and could cut the nation's health bill by up to \$356 million a year, the team concluded.

In 1990, Dong sent Boots the results. "Over the next 4 years, Boots waged an energetic campaign to discredit the study and prevent publication of the drafts Dong and her colleagues sent to them for comment, claiming that the study was seriously flawed," asserts JAMA deputy editor Drummond Rennie.

Two years ago, as JAMA prepared to publish the findings, Dong withdrew the study—because Knoll threatened to sue the university and the researchers for violating the nondisclosure clause of their contract. Then, a year ago, the Wall Street Journal ran a detailed account of the dispute.

That article broke the impasse. The company decided to release the study, in part because the account "had been accepted as fact" by many doctors and publication of the report itself would allow them to make up their own minds about its validity, Knoll President Carter H. Eckert wrote in a letter to JAMA.

There was another reason, too, he wrote: "... we had gained a better understanding of the importance of supporting academic freedom and the peer review process. . . ."

A separate study of life science researchers conducted by scientists at Harvard Medical School in Boston and reported in the same issue of JAMA found that 20 percent of 2,197 respondents reported having withheld results.

The April 16 JAMA also contains this ad placed by one of Knoll's rivals: "If you're still prescribing Synthroid, here's a dose of reality."
— S. Sternberg

Uterus makes a marijuanalike compound

In recent years, researchers have found that mammalian brains can make a compound, anandamide, whose effects resemble those of THC, the active component of marijuana (SN: 2/6/93, p. 88).

Yet the brain may not be the only anandamide producer around, or the most impressive. According to studies of pregnant mice, the uterus can synthesize this compound in massive quantities—possibly to ensure that an embryo lodges in the uterine wall at the appropriate time.

"Anandamide may determine the window of uterine receptivity for implantation," says S.K. Dey of the University of Kansas Medical Center in Kansas City.

In past studies, Dey and his colleagues found that early mouse embryos display a cell surface protein that can interact with anandamide and that exposure to the compound can impair or halt development of the embryos.

Those observations prompted Dey, Patricia C. Schmid of the University of Minnesota in Austin, and their colleagues to investigate whether the uteri of pregnant mice make anandamide.

In the April 15 *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES*, the scientists report that tissue from such uteri harbors anandamide in amounts far greater than those found in mouse

brains. In fact, says Dey, the anandamide concentrations are "the highest found in any tissue of any species."

The group also reports that anandamide concentrations in the uterus change during the early stages of a mouse's pregnancy, peaking at the same time that the uterus becomes resistant to the embryo's implantation.

The researchers further found that they could prevent embryos of recently impregnated mice from lodging in the uterus by implanting in the mice a pump that continuously releases a synthetic, anandamidelike compound.

Dey speculates that some cases of infertility result when a woman's uterus makes too much anandamide or her embryos are abnormally sensitive to the compound.

The high uterine concentrations of anandamide are "quite surprising, but if they are correct, then we have something very novel concerning pregnancy," comments Raphael Mechoulam of Hebrew University of Jerusalem, the discoverer of both THC and anandamide.

Does this new work imply that marijuana smoking alters fertility? Mechoulam is skeptical, arguing that the many epidemiological studies done on marijuana smoking have not revealed any such link.
— J. Travis