

Book Touts Dilantin for Depression

But researchers and the drug's manufacturer deny Dilantin's value as an antidepressant

In 1957, Jack Dreyfus, the 43-year-old founder of the Dreyfus Fund, was a Wall Street prodigy. That year, however, the multimillionaire slipped into an inexplicable and debilitating depression. By his own account, he was haunted by an overactive mind that "never gave me rest and was always occupied with thoughts related to anger and fear. And the fear was the worst."

Dreyfus swung in and out of depression for the next several years. Then he became aware of something that would radically change his life. He learned that epileptic seizures have long been commonly controlled by a prescription drug called Dilantin and he reasoned that his "turned-on mind," as he called it, might be caused by faulty "electrical activity" in the body akin to that during a seizure. Dreyfus took Dilantin and his depression disappeared as quickly as it had come.

Astonished and elated at his dramatic recovery, he became so convinced that Dilantin has powers beyond its anti-epileptic use that he retired as president of the Dreyfus Fund to devote 15 years and \$15 million to persuade others of his opinion. He has taken his case to top government officials over the years and met with former President Nixon, three secretaries of the former Department of Health, Education, and Welfare, two Food and Drug Administration commissioners, and a Surgeon General. In a last-ditch effort to attract government and public attention to Dilantin, Dreyfus has written *A Remarkable Medicine Has Been Overlooked*. The book is being promoted with the largest advertising budget in the history of its publisher, Simon and Schuster, at a sum of \$2 million—paid by Dreyfus himself.

Although Dreyfus is genuinely convinced that there is abundant scientific evidence which demonstrates Dilantin's versatility, authorities deny it has a wide range of uses, particularly in treating psychiatric disorders. It appears that Dreyfus' efforts to promote Dilantin amount to a costly private obsession, a crusade that has had little influence on the federal government or the medical community, much to Dreyfus' frustration.

In his book, Dreyfus charges that the federal drug approval process is seriously flawed. Specifically, he wants the

FDA to broaden the list of federally sanctioned uses of Dilantin, a phenytoin sodium compound produced principally by Parke-Davis. Physicians can prescribe drugs for uses other than those officially listed with the FDA, but Dreyfus argues that doctors are less inclined to do so without the agency's approval. The agency, however, cannot expand the list of approvals without sufficient evidence from clinical trials, which are usually conducted by the drug manufacturer. Dreyfus contends that, in the case of Dilantin, Parke-Davis has little incentive to conduct more research because the company's patents on the drug have expired.



Jack Dreyfus

The book includes an account of how Dilantin relieved Dreyfus' own depression, and an extensive bibliography of the scientific literature related to the drug. Dreyfus maintains that the case studies and clinical trials published—though many of them were not controlled or double-blind—should be more than enough evidence to persuade the FDA to list Dilantin as a "stabilizer of bioelectrical activity," rather than only as an anticonvulsant.

He believes that his opinion of Dilantin is buttressed by the results of a double-blind, controlled study in which Dilantin was tested on 11 inmates of a Massachusetts county jail in 1966. The study was one of the several he himself funded at various institutions. Results of the Worcester jail study showed that 10 of the 11 subjects, whose dominant disorders were an overactive mind and excessive anger and fear, improved after taking Dilantin. The findings were re-

ported at a 1967 meeting of the American College of Neuropharmacology and recounted in the *International Journal of Neuropsychiatry* the same year.

Scientists and Parke-Davis officials acknowledge Dreyfus' sincerity but criticize his contentions. Parke-Davis officials dispute Dreyfus' assertion that patent expiration has discouraged research on Dilantin. They say the company, in fact, never held a patent on the drug compound. Moreover, they explain that the firm has maintained continuous, though limited, interest in Dilantin, which is demonstrated by their plans to apply to FDA for a listing of two additional uses of Dilantin. (The new uses are for the treatment of cardiac arrhythmias and head trauma. Dilantin has long been used by physicians to treat erratic heart beats.)

Parke-Davis officials say the company has no plans to study Dilantin for treatment in depression or other mental disorders. James Weir, company vice president of regulatory and scientific affairs, said, "There are already drugs on the market that are well studied for depression." He said, "Jack Dreyfus feels that Dilantin has helped him. I'm happy for Jack, but he takes a simplistic view of depression. For 15 years and \$15 million he's been banging his head against the wall."

Paula Botstein, an assistant to the director of the Bureau of Drugs at FDA, says that Dilantin may have other uses but that "It's hard to tell from anecdotal evidence."

According to FDA records, a 15-member agency committee on neuropharmacology concluded in 1973 that "the drug is not proven to be useful at this time [in nonpsychotic disorders] . . . that out of all the studies publicized thus far there has been little promising information."

Dreyfus has gone to great lengths to attract attention to Dilantin, but with his book now in print, he says he is giving up the battle to bring Dilantin to the government's attention.

Since its release in September, the book has been advertised in major newspapers and magazines and on television. The unusual jacket of the book displays an open letter to President Reagan, urging him to remedy the "flaw" in the drug approval process. "I'm not trying to

hype the book," remarked Dreyfus, who said he has no financial interest in Dilantin. "I'm trying to get the information out there. I just want the doctors and the public to know about Dilantin."

Simon and Schuster marketing director Albert Reuben described book sales as "okay." He said that the book "is nowhere near a best seller, but it's not a dog either." There are now 120,000 copies in print.

According to a spokeswoman for Simon and Schuster, an author rarely contributes money to tout his own book. It is even more unusual, perhaps unprecedented, Julia Knickerbocker said, that a writer would dole out \$2 million. Given Dreyfus' personal subsidy of his book's promotion and agreement by many scientists that his assertions are premised on weak evidence, it appears that a major publisher has behaved like a vanity

press, he said in an interview. The study was not published.

After the Columbia study, Dreyfus also funded clinical trials at Johns Hopkins that produced mixed results. In one well-controlled, published study, Dilantin was clearly effective in treating a group of 30 patients with narrowly defined psychiatric disorders.

Yet in another experiment on a group of patients with more general mental and emotional problems, Dilantin was found to be no more effective than phenobarbital. The experiment was a double-blind comparison and reported in *Pharmacologia* by E. H. Uhlenhuth, who was then at Johns Hopkins and is now a professor at the University of Chicago. He noted in its introduction that Dreyfus and his medical adviser "have summarized and extensively documented the high level of enthusiasm, sustained by many authors

tin studies for Dreyfus that were negative, said, "It's possible that Dilantin does work, but only in a small group of people." Defining such a group would be experimentally difficult, but not impossible, because of the large sample size required and the complications of placebo effect, he said.

A researcher at the National Institute of Mental Health also speculates that Dilantin might have some effect. Robert Post, chief of the psychobiology section, is currently testing another anticonvulsant called carbamazepine for its effects on depression and mania. Carbamazepine, which has a different mode of action from Dilantin's and is chemically dissimilar, has shown efficacy in some patients, Post said. He plans to test Dilantin on this group also. He said he receives no funding from Dreyfus and has not read his book.

Even before some of the university studies were complete, Dreyfus began meeting with federal officials, armed with the Worcester jail study results as his best evidence. But just what Dreyfus wanted the government to do with the information he offered was vaguely defined. "It wasn't clear to me what to ask for," Dreyfus told *Science*. "I had hoped the government would take over the responsibility."

Although Dreyfus persisted in his efforts, he failed to convince the FDA or Parke-Davis of Dilantin's purported range of effects. The FDA, in 1972, went as far as to hold a 2-day conference on the drug at which Dreyfus and a medical adviser presented their evidence. Later, Dreyfus even spent a weekend retreat with Caspar Weinberger, then HEW secretary, for the sole purpose of discussing Dilantin. Dreyfus said little came of either meeting.

Dreyfus said he is not angry with the drug company or the FDA, but he is certainly frustrated. "I wish I could find a villain." He said, "Parke-Davis has slept solidly through all of this." Perhaps Dreyfus could have furthered his cause for Dilantin more by sponsoring a truly large-scale clinical trial rather than by pouring \$2 million into book promotions. A Parke-Davis spokesman estimated that a good study, which would provide sufficient data to apply to FDA for a new listing, would cost at least \$1 million. Dreyfus quickly dismissed the suggestion of funding such a project. Another clinical trial, he said, would provide more studies for the FDA and the doctors to ignore." Dreyfus, now 68, said, "If I go further, I'll look like a nut. I probably look like that to some already."—MARJORIE SUN

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press. Knickerbocker disagreed. "With or without the [Dreyfus] money we would have published the book," she said. "From a popular point of view, it's an interesting book. Dreyfus may be mistaken scientifically but he deserves to be heard." The backing of a leading publisher, however, lends credibility to the information in the Dreyfus book.

After his own recovery, Dreyfus persuaded several of his friends who complained of depression and other mood disorders to take Dilantin, which was prescribed to them by Dreyfus' own doctor. They also found it effective.

Encouraged by these results, Dreyfus redirected the Dreyfus Medical Foundation, which is funded solely by his own money, to concentrate its activities on sponsoring studies on Dilantin and disseminating information on the drug. According to Dreyfus, he received few results from some of the studies.

The investigators argue that Dreyfus simply did not get the results he hoped for. "Dreyfus is not a charlatan. He really firmly believes in Dilantin. But Dreyfus wanted us to come up with an answer he wanted whether he realized it or not," said Sidney Malitz, acting chairman of the psychiatry department at Columbia Presbyterian Hospital. In the late 1960's, Malitz conducted an uncontrolled pilot study, sponsored by Dreyfus, on a "sufficient number of patients that convinced us Dilantin was not prom-

over a long span of years," about the use of Dilantin in psychiatric disorders. But "In view of these developments, it is surprising to find that only six controlled studies on this subject have been completed," the report said. Jack Dreyfus is "overenthusiastic," Uhlenhuth said in an interview.

Although Dreyfus does include some negative studies in the extensive bibliography in his book, it is curious that Uhlenhuth's findings were not prominently cited, given the dearth of well-designed clinical trials on Dilantin's effects on psychiatric disorders. (The study is noted in fine print among the thousands of reports on Dilantin listed in the back of the book.)

Dreyfus said in an interview that the omission "was not malicious. The evidence was just so strong for Dilantin. If 1,000 people see an elephant jump over a fence and one person doesn't see it, that doesn't mean that the elephant didn't jump." He said, "People talk about controlled experiments only in terms of double blind. But what if you give a drug to someone who has been suffering for 20 years and he recovers? Doesn't that tell you something?"

Although Dilantin may not possess the virtues that Dreyfus ascribes to it, scientists do not completely dismiss Dilantin as a useless medication for mental disorders. Donald Klein, psychiatry professor at Columbia, who has conducted Dilan-