How Safe Is Bendectin?

An FDA panel sees no evidence that it causes birth defects. Lawyers say they will sue anyway

The safety of Bendectin, a drug taken for morning sickness in pregnancy, has become the subject of an emotional and intense debate among parents, lawyers, and medical scientists. Lawyers claim Bendectin is a new thalidomide and are seeking women who took the drug and bore deformed children to join in lawsuits against Richardson-Merrell Inc., the drug's manufacturer. A number of scientists are saying that the drug has never been shown to be dangerous to fetuses and, in the absence of any such evidence, the lawsuits are unwarranted.

What is really at issue is the more subtle question of how safe is safe. Does lack of evidence that a drug is harmful mean that it is not? Can a manufacturer be held liable for damages when scientists say they have a "residual uncertainty" about a product's safety? These questions go far beyond the specifics of the Bendectin case and extend to virtually every drug and possibly toxic substance to which people are exposed. For this reason, the Bendectin story has become a symbol of the quandaries that arise when science is unable to provide definitive answers to questions of public health.

Bendectin is one of the more commonly used drugs during pregnancy. Richardson-Merrell estimates that 25 percent of pregnant women in the United States take the drug, and it is popular in other countries including Germany, Canada, and Great Britain. Some doctors, in fact, are said to hand out prescriptions for Bendectin along with prescriptions for prenatal vitamins.

Although Bendectin has been on the market for 23 years, doubts about its safety were voiced only in the past 2 years. They began in the medical community when Kenneth Rothman of the Harvard School of Public Health found a weak association between Bendectin and congenital heart defects. Last winter, the doubts about Bendectin reached the general public as a result of a highly publicized trial in Florida in which the flamboyant lawyer Melvin Belli represented the parents of a deformed boy whose mother had taken the drug.

In response to intense public interest in Bendectin, the Food and Drug Administration (FDA) moved up its scheduled hearings on the drug's safety from October to September. On 15 and 16 September, an FDA panel met in a hot, stuffy room crowded with lawyers to review animal data and 13 epidemiologic studies. It unanimously concluded that there is no demonstrated association between Bendectin and birth defects. However, the panel noted that because there is no way to prove absolute safety, there is a "residual uncertainty" about the drug's effects on fetuses.

The 13 studies reviewed by the FDA panel varied enormously in design and reliability, and most had an unresolvable limitation. Women were asked, usually after their babies were born, whether they had taken Bendectin. Hershel Jick of the Boston Collaborative Drug Surveillance Program observes that the "recall" method introduces an enormous problem of bias. Women with normal babies may forget they took the drug and those with malformed babies may be more likely to remember—or vice versa. The bias is essentially unmeasurable.

Only two studies circumvented this problem. One was done by Jick himself, who examined computerized medical records at the Group Health Cooperative at Puget Sound for nearly 6000 pregnant women, 40 percent of whom were recorded as filling Bendectin prescriptions. He saw no indication that the drug caused an increase in any particular birth defect, including those that have been suspected of being caused by Bendectin, such as limb deformities and cleft lips or cleft palates.

The other study that is free of recall bias is one by Richard W. Smithells of the University of Leeds in England. Smithells also gauged Bendectin use on the basis of filled prescriptions. He reports no evidence of an increase in birth defects in general or in any specific type of birth defect in 2,000 women who took the drug as compared to 11,000 women who did not.

Ralph D'Agostino, a statistician at Boston University and an FDA panel member, argues, however, that from a statistical point of view it is more valuable to look at data from studies that focus on specific defects and then see if women who gave birth to children with these defects are more likely to have taken Bendectin. The method of looking at a whole spectrum of birth defects usually yields small numbers of babies with particular defects. For example, Jick found only 12 babies with limb deformities in his sample.

Most of the studies that focused on particular birth defects showed no relation between the defects and Bendectin. Two teams of researchers looked at specific defects, however, and found a slight association with Bendectin use. In one study, led by Rothman, there were weak associations between heart defects and aspirin, antibiotics, and Bendectin. He describes his results as at best "exploratory," not to be taken as indicating that Bendectin causes heart defects. He mentions particularly the problem of recall bias, since women were given an open-ended questionnaire about drug use.

Jean Golding of the University of Bristol in England asked doctors what they had prescribed for mothers of babies with cleft lips or palates and for mothers of normal babies, and found that the number of reported Bendectin prescriptions was slightly higher for mothers of babies with these birth defects. But Golding is ambivalent about her results because of the bias introduced by her method of ascertaining Bendectin use.

In the end, the discussion of Bendectin's safety came down to reasoning that more studies have been done on Bendectin than on any other prescription or nonprescription drug taken by pregnant women and nothing has shown that the drug is dangerous. Scientists at the FDA meeting also said that every agent that is known to cause birth defects causes a recognizable syndrome. No such syndrome has been associated with Bendectin. Since 30 million pregnant women have taken the drug, Jick says, he "would find it a shocking fluke if something were going on with the drug that we have missed."

The FDA panel did express concern, however, that the drug was associated with birth defects in the studies of Golding and Rothman, even though these findings were not confirmed by other studies. The panel noted that Bendectin is probably overprescribed. Certainly, scientists at the meeting argued, if the

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drug is to be used only for intractable nausea and vomiting, 25 percent of the pregnant women in this country (and 40 percent in Puget Sound) should not be taking it. Panel member Brian Little, a professor of obstetrics and gynecology at Case Western Reserve University, estimated that fewer than 10 percent of pregnant women should require Bendectin.

Belli says the FDA panel's decisions will not deter the lawsuits pending against Richardson-Merrell. "We will not rely on the FDA at all. We're going ahead with our own proof [that Bendectin causes birth defects]," he declared. His proof consists of a list of women who took the drug during pregnancy and bore children with limb defects. In addition, Belli has his own expert witnesses. But epidemiologists say a list of deformed children is not proof. Every year, about 90,000 babies are born with serious birth defects, and 3,000 of them have limb defects. By chance alone, then, if 25 percent of pregnant women take Bendectin, 750 babies with limb defects should be born each year to women who took the drug.

To find such babies, Belli has placed ads in U.S. newspapers and has traveled to England and Germany. He says he is thus far suing Richardson-Merrell on behalf of 75 women and knows of at least 125 Bendectin lawsuits, in addition to his own, that are going to trial. A Richardson-Merrell spokesman says, however, that only 36 lawsuits have been filed.

The hundreds of millions of dollars riding on the Bendectin suits drew a crowd of lawyers to the FDA meeting. Their vociferous questioning of the scientists who testified at the meeting so antagonized Robert Irvine, director of communications for Richardson-Merrell, that every time a lawyer was recognized, Irvine jumped up and pointed out that the questioner was an attorney who was engaged in litigation with his company. "I don't think this FDA hearing should be used for the process of discovery," Irvine kept saying. Finally, FDA panel chairman David Archer, of the University of Pittsburgh School of Medicine, declared that all further questions must be submitted to him in writing and he would then determine whether they would be answered.

One thing Belli and the other lawyers involved in litigation with Richardson-Merrell believe they have going for them is the company's past reputation. In the early 1960's the company tried to introduce thalidomide into the United States and marketed the drug in Canada. It was successfully sued on behalf of a number of U.S. children whose mothers were given thalidomide by doctors who received the drug as free samples, and on behalf of Canadian thalidomide children. The settlements ranged from $100,000 to $999,000.

Just before thalidomide, in 1960, Richardson-Merrell marketed Mer-29, a cholesterol-lowering drug that it envisioned millions of Americans taking each day like a vitamin pill. But Mer-29 turned out to cause cataracts and was withdrawn from the market in 1962. Richardson-Merrell was indicted for making false, fictitious, and fraudulent statements to the FDA about Mer-29 and was fined $80,000. Following the criminal indictment, 500 civil suits were filed by injured persons and Richardson-Merrell ended up paying $200 million in damages.

Public agitation about Bendectin began last October with an article in the *National Enquirer* that also compared the drug to thalidomide and included pictures of babies with deformed arms or legs. Prominently featured in the article was David Mekdeci, the Orlando, Florida, boy who was to be the subject of the first Bendectin lawsuit.

In January 1980 the trial involving David Mekdeci took place. The boy's parents, Michael and Elizabeth Mekdeci, sued Richardson-Merrell for $12 million. The Florida jury concluded that nothing should be awarded to the boy and denied any money to his parents for damages. It did, however, award the parents $20,000 for medical expenses. In May, Federal Judge Walter E. Hoffman ordered a new trial because, he said, the jury's verdict was "inconsistent." He argued that if the child was not damaged by Bendectin, the parents should not be awarded anything. A retrial is scheduled for January 1981, but Belli, "for reasons of honor and self-respect," asked not to represent the family the second time around. Belli calls Mrs. Mekdeci "a very difficult woman to work with. Besides, we've got much better cases."

The FDA panel had an opportunity to hear four of the expert witnesses who testified for the plaintiffs in the Florida trial. Their data, said scientists who attended the meeting, were hardly convincing. FDA panel member Gordon Avery, of the Children's Hospital in Washington, D.C., said that "As far as I'm concerned, the purpose of the hearing was to objectively view the scientific data. None of these people brought anything other than special pleading."

These expert witnesses included William McBride of the Women's Hospital in Sydney, Australia, who was paid $5,000 a day to testify in Orlando. In contrast, Richardson-Merrell, pays witnesses $250 to $500 a day, and the most it has ever paid is $1000 a day. McBride was one of the first to suspect that thalidomide caused birth defects. He contends that Bendectin, too, causes deformed arms and legs, and he said at the trial that, in his opinion, Bendectin caused David Mekdeci's malformations. For much of his talk at the FDA meeting, McBride dwelt on the effects of thalidomide, leading Avery to say, "Dr. McBride, you have convinced me that thalidomide is a teratogen but I must in my own mind focus on the drugs that are in Bendectin."

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Another of Belli's witnesses was Beverly Paigen of Roswell Park Memorial Institute. Paigen stressed that she is a cancer researcher, not a teratologist. Nonetheless, she concluded that Bendectin caused birth defects in 5 of 1000 babies whose mothers took the drug. D'Agostino commented to *Science* that "Her [Paigen's] interpretation of the data just is not warranted." He remarked, "The committee as a whole took them [Belli's four witnesses] as a set of presentations that didn't necessarily appear to contribute anything to the real discussion."

Despite the FDA panel's cautions and carefully worded conclusions, the forthcoming court cases will probably convince many women that Bendectin may cause birth defects. As a result of fear of Bendectin, Little predicts, doctors may start prescribing different drugs to combat nausea and vomiting, even though extremely little is known about alternative drugs. Despite the FDA panel's residual uncertainty about Bendectin's safety, it remains the best studied drug taken by pregnant women. "I wish we knew as much about aspirin," said one scientist at the meeting.

—GINA BARI KOLATA