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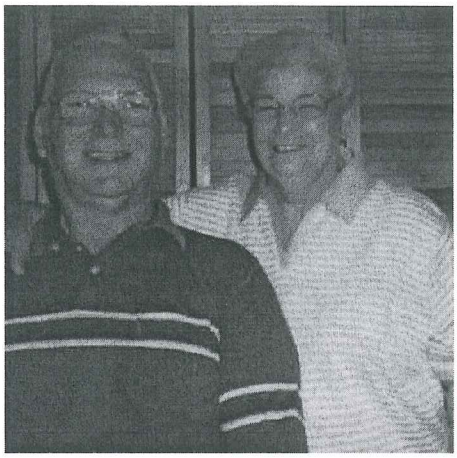

Removal of Diabetes Drug Meets With Mixed Feelings

By HOLCOMB B. NOBLE

Shirley Griggs, shown with her husband, Jerry, said the drug destroyed her liver and left her in constant pain

The removal of the diabetes drug Rezulin from the market did not come soon enough to help Monica George, a 68-year-old former nurse in Rockville, Md.: It had already caused her death, her daughters said. But the drug's removal upset Frank Hopkins, a Virginia horse-farm owner, who said it greatly improved his health and brought his diabetes under control.

The removal of the drug by the Food and Drug Administration last week brought anger, confusion and a stream of questions. Doctors and patients alike asked whether the agency had approved the drug too quickly, without regard to the severe liver damage it could cause. When liver failure and deaths began to occur, did the agency act too slowly in removing the drug? If so, why?

The F.D.A. approved Rezulin in March 1997 as the first of a class of drugs called insulin sensitizers that help the body respond more effectively to its own insulin production, thereby reducing the patients' need to give themselves insulin shots. It was prescribed heavily and almost immediately: By last week 1.5 million patients had used it, and it had generated $1.7 billion in sales for the manufacturer, Parke-Davis, a division of Warner-Lambert.

Critics say the evidence was clear in the clinical trials that Rezulin could cause severe liver problems but that the agency had approved it for marketing without proper warnings or recommendations that it be monitored. Eight months later, after problems arose, warnings of liver problems and recommendations that patients be closely monitored were issued. By March of last year 26 deaths had occurred and by last week the number had risen to 63, with a total of 90 cases of liver failures reported and 14 of them resulting in a need for transplants. The F.D.A. advised patients to talk to their doctors about what they should do next. Since Rezulin was introduced, two similar medications have been put on the market with fewer risk, Actos and Avandia. The F.D.A. defends its actions in both approving and then withdrawing the drug, saying it was unfair to suggest in hindsight that it could have predicted what happened. In some cases, the agency says, the liver failure happened so fast that even close monitoring would not have prevented it. Many patients interviewed were angry that the drug was approved so quickly, but in the end they generally regarded the drug's removal as good news.

"This needed to happen," said Elaine M. Shaw, a special-education nurse in Charlottesville, Va., and one of Monica George's three daughters. "It does not bring my mother back, but I think it will save lives." Ms. Shaw said that her mother, a geriatric nurse, was "savvy about her own liver function and she knew she had elevated liver enzymes -- but

she did not know there were concerns about liver toxicity with the new drug."

Mrs. George was a "vibrant, healthy woman, in a good place with her life, traveling, enjoying grandchildren," her daughter said, when she was put on Rezulin in November 1997. But she then began to complain of fatigue, weight gain, poor circulation and other symptoms associated with liver problems. Her doctor at the time, Ms. Shaw said, told her mother that fatigue was normal, but he did not check her liver function and kept her on Rezulin. Mrs. George switched doctors and was promptly taken off the drug in August 1998, but after several weeks of intense suffering she died of severe liver damage, Ms. Shaw said.

Last Wednesday, the day after the F.D.A. acted, Elaine Shaw and her sisters, Andrea Shaw and Donna Louise George Storey, filed suit against the first doctor and Warner-Lambert/Parke-Davis. In the suit, they said the company's clinical trials showed the drug could cause "serious liver damage leading to death or requiring liver transplant." The daughters said that Rezulin was initially marketed without warnings or explanations sufficient to reflect the severity of possible liver problems, but that eight months later the company added information about possible toxic effects and recommended monitoring patients' liver conditions. The next month, the suit says, the labeling was changed again to say that "cases of liver failure leading to death and liver transplants had been reported, and that injury occurred after both short-term and long-term use of Rezulin."

Mrs. Shaw's lawyers, at Littlepage & Associates of Houston, said the company deliberately withheld important information needed by doctors and their patients.

Jason Ford, a spokesman for Warner-Lambert, said he could not comment on the specifics of the Monica George lawsuit. But in regard to claims of adverse reactions, he said the company had "adequately warned about the risks associated with the product," and he said that it intended "to vigorously defend any lawsuits."

For Shirley Griggs, 66, of Smithville, Mo., the adverse reaction was severe. She said that after she was put on Rezulin, she gained 43 pounds, but that her doctors failed initially to detect liver damage. By the time she was taken off the drug, she said, she was in constant pain and her liver was crippled. She is now on a transplant list but "thousands are ahead of me," she said.

In any case, there is little doubt that the drug helped some. Frank Hopkins, who raises racehorses in Darlington, Md., said that when his blood-sugar levels became high and his doctors could not bring it down, they referred him to Dr. Christopher D. Saudek, head of the diabetes center and professor of medicine at Johns Hopkins School of Medicine. Dr. Saudek, he said, put him on Rezulin in 1998, which brought the blood sugar down, but he also checked blood samples and liver function monthly. Mr. Hopkins said he was upset that the drug was being withdrawn. "I think the number of people who have received a negative reaction is so minimal, so why should the rest of us have to suffer?" he said. But he said he was relieved to learn that similar, but less risky drugs had become available.

Dr. Saudek said that in general, the insulin sensitizers are an "exciting new class of drugs." Dr. Richard Beaser, at the Joslin Diabetes Center in Boston, and others said patients were rightfully angry and confused but that it was important not to allow it to erode confidence in the drug-approval process. "I am concerned about the process and so are my patients. If it was legitimate, fine, but we need reassurance," he said. "And, if it was not, there needs to be an investigation to find out why and restore confidence in the system."

Carol Whitty, 54, a first-grade teacher of Walpole, Mass., has not lost confidence. "Three years ago, I was giving myself insulin injections, once in the morning, once at night," she said. "This is not really such an easy thing." Dr. James Rosenzweig at the Joslin clinic put her on Rezulin.

"Within just a few months," she said, "I was able to come off the shots completely." For Ms. Whitty, Rezulin's removal was not a problem. She simply switched to the more recently introduced Actos, of the same type that she said had changed her life. "I can't tell you how grateful I am," she said.

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