Frances Oldham Kelsey:

FDA Medical Reviewer Leaves Her Mark on History

By Linda Bren http://www.fda.gov/fdac/features/2001/201_kelsey.html

It was early 1942 and war was raging in the jungles of the Pacific. In addition to fighting the Japanese, Allied troops found themselves under attack by malaria-carrying mosquitoes. The search was on for an effective quinine substitute to combat the disease. A possible treatment--in the form of a dark, inky substance--arrived for testing in the pharmacology department at the University of Chicago. Pharmacologist Frances Oldham Kelsey, like many other university researchers throughout the country, had enlisted in the search for synthetic cures for malaria. As it turned out, the inky substance had been sent by a veterinarian in Texas. "He said that he had just tried it on his secretary without ill effects," says Kelsey, "and he planned next to try it on cattle. It showed the relative value placed on women and cattle in Texas at that time," Kelsey says with amusement.

The war ended without finding a good substitute for quinine. But Kelsey did learn something valuable from the experience. She learned that rabbits metabolized quinine rapidly, but pregnant rabbits had less ability to break down the drug, and embryonic rabbits could not break it down at all. She also learned that drugs could pass through the placental barrier between mother and unborn child. These insights would serve Kelsey well some 15 years later when in early 1960, as a new Food and Drug Administration employee, she was asked to evaluate a drug most thought was harmless. That drug was thalidomide.

Although pressured by the manufacturer to quickly approve a drug already in widespread use throughout the rest of the world, Kelsey held her ground. When she repeatedly asked for more data and effectively forestalled the approval of thalidomide, Kelsey did more than keep a dangerous drug off the market. She set into motion a series of events that would forever change the way drugs are tested, evaluated, and introduced in America.

In recognition of Kelsey's vigilance, President John F. Kennedy, on Aug. 7, 1962, presented her with the highest honor that can be bestowed upon a U.S. civilian: the medal for Distinguished Federal Civilian Service.

The Thalidomide Tragedy

All they wanted was a good night's sleep, and a drug called thalidomide gave it to them. It brought a quick, natural sleep for millions of people who had trouble drifting off, and it also gave pregnant women relief from morning sickness. The drug's German manufacturer Grunenthal claimed it was non-addictive, caused no hangover, and was safe for pregnant women. And, unlike barbiturates, its lack of toxicity made it a poor choice for a suicide attempt. By 1957, thalidomide was sold over-the-counter in Germany. By 1960, it was sold throughout Europe and South America, in Canada, and in many other parts of the world. To introduce it into the United States, the Richardson-Merrell pharmaceutical company of Cincinnati submitted an application to FDA in September 1960 to sell thalidomide under the brand name Kevadon.

The application was assigned to medical officer Kelsey, who had joined FDA just one month earlier. It was her first drug review assignment.

Under the law at that time, FDA had 60 days to review a drug application. If an FDA medical officer notified the company that the application was incomplete, it was considered withdrawn and the company would have to resubmit it with additional data. With each resubmission, the 60-day clock would start again.

Kelsey had concerns about the drug from the beginning. So did the pharmacologist and chemist who assisted Kelsey in the drug review. The chronic toxicity studies were not long enough, the absorption and excretion data were inadequate, and the manufacturing controls had shortcomings. "We were concerned about the non-absorption," says Kelsey. "That you could give enormous amounts, both to animals and humans, without toxicity. We felt that there might be conditions, illnesses, or other drugs that might change the absorption, and toxic effects might appear." After Kelsey detailed these deficiencies in a letter to Richardson-Merrell, the company sent in additional information--but not enough to satisfy Kelsey. "The clinical reports were more on the nature of testimonials," says Kelsey, "rather than the results of well-designed, well-executed studies."

Kelsey continued to request more data to show the drug's safety, and with each request, the 60-day clock restarted. Dr. Joseph Murray, Richardson-Merrell's representative, grew increasingly frustrated. He made repeated phone calls and personal visits to Kelsey, and complained to her superiors that she was unreasonable and nit-picking, and that she was delaying the drug's approval unnecessarily. But Kelsey did not cave under the pressure. "I think I always accepted the fact that one was going to get bullied and pressured by industry," says Kelsey. "It was understandable that the companies were very anxious to get their drugs approved."

In December of 1960, three months after Richardson-Merrell submitted its application, the British Medical Journal published a letter from a physician, Leslie Florence, who had prescribed thalidomide to his patients. Florence reported seeing cases of peripheral neuritis, a painful tingling of the arms and feet, in patients who had taken the drug over a long period of time. After reading the journal letter, Kelsey immediately contacted Richardson-Merrell, requesting further information on this serious side effect. Recalling how quinine had affected adult rabbits and fetuses differently, Kelsey wondered what effects thalidomide may have if used during pregnancy. She suspected that a drug that could damage nerves could also affect a developing fetus. Her suspicions soon proved to be grimly accurate.

European physicians began reporting a disturbing phenomenon. A growing number of women were giving birth to terribly deformed babies. Some had abnormally short limbs, with toes sprouting directly from the hips, and flipper-like arms--a condition known as phocomelia. Others had malformed internal organs or eye and ear defects. Women were miscarrying or giving birth to infants who died shortly after.

At first, no one knew the cause. But by November 1961, a German pediatrician, Widukind Lenz, determined it was thalidomide. Upon questioning his patients, Lenz found that 50 percent of the mothers with deformed children had taken thalidomide in the first trimester of pregnancy.

Lenz warned the German manufacturer, Chemie Grunenthal, about the dangers of thalidomide. Ten days later, German health authorities pulled the drug from the market--against the company's wishes. Other countries closely followed its lead. Chemie Grunenthal continued to dispute the findings, but in March 1962, Richardson-Merrill withdrew its application from FDA. Unfortunately, by then, it was too late for many.

More than 10,000 children in 46 countries were estimated to have been born with deformities as a consequence of thalidomide use. The damage in the United States was small by comparison, but no less devastating to the 17 children born in America with thalidomide-associated deformities.

Richardson-Merrell had distributed more than 2.5 million thalidomide tablets to more than 1,000 doctors throughout the United States on what was called an investigational basis. The doctors, in turn, gave thalidomide to nearly 20,000 patients, several hundred of whom were pregnant women.

Kelsey's Early Career

Born in 1914 in Cobble Hill on Vancouver Island, British Columbia, Kelsey graduated from high school at age 15 and went on to earn a BSc in 1934 from McGill University in Montreal. After earning her MSc at McGill in pharmacology in 1935, Kelsey, became assistant to E. M. K. Geiling, MD, who was starting up a new pharmacology department at the University of Chicago.

In 1937, Kelsey's second year at the University of Chicago, FDA asked Geiling to help determine why people were dying after they drank "Elixir Sulfanilamide." Sulfanilamide, introduced in 1935, was extremely effective in fighting bacterial infections. But the sulfanilamide pills were pretty unpalatable. The Massengill Company asked its chemist to find a liquid solution in which the drug could be dissolved, making it more pleasant-tasting, especially to children. "The solution was put right on the market with a little pink coloring and a little cherry flavoring, and it sold like wildfire," says Kelsey. Under the law at that time, the Food and Drugs Act of 1906, a company could sell a drug without showing its safety. Soon after the elixir hit the market, reports of deaths involving the solution started flowing in--but no one was sure whether it was the sulfanilamide or the solvent that was toxic. As a student of Geiling, Kelsey helped conduct animal studies to find out which was the toxic element. After testing various combinations of sulfanilamide and solvent, it became apparent that the toxin was the solvent--diethylene glycol--which is similar to antifreeze.

The immediate outcome of Elixir Sulfanilamide was tragic--it caused 107 deaths, many of them in children. It also led to the suicide of Massengill's chemist and to a fine of $26,100 levied against Massengill, the highest that was legally allowed at the time. Since the manufacturer was not required to demonstrate its product's safety, FDA could not hold Massengill accountable for the deaths. The company could only be fined for "misbranding" its product. An elixir, by definition, contained alcohol, but there was no alcohol present in Elixir Sulfanilamide.

The long-term effects were also remarkable. Public outrage spurred the passage of the Federal Food, Drug, and Cosmetic Act of 1938. The new drug law required companies to show evidence of safety before their product could be marketed, and warnings of the potential hazards of drugs were required. And for the first time, medical devices and cosmetics were included in FDA's authority.

In the same year the new drug law went into effect, Kelsey received her PhD in pharmacology from the University of Chicago and joined the faculty. In 1960, Kelsey was offered a position at FDA in Washington, D.C. It was there that she would leave her mark on history.

The Road to Stronger Drug Laws

The headline read "'Heroine' of FDA Keeps Bad Drug Off of Market." The story appeared on the front page of The Washington Post on July 15, 1962. Reporter Morton Mintz told the tale of "how the skepticism and stubbornness of a Government physician prevented what could have been an appalling American tragedy, the birth of hundreds or indeed thousands of armless and legless children." Mintz's article catapulted Kelsey to stardom. It also inspired a flurry of follow-up articles on drug control in The New York Times and other media.

In the wake of the furor these articles created, the American public soon came to realize how narrowly they had averted a major tragedy. And politicians who had been fighting for years for tighter drug controls were finally taken seriously. A controversial bill introduced by Sen. Estes Kefauver several years earlier was resurrected from its congressional committee graveyard and rewritten. President Kennedy signed the bill generally known as the Kefauver-Harris Amendments into law on Oct. 10, 1962. This landmark drug law, which modified the earlier Federal Food, Drug, and Cosmetic Act of 1938, strengthened FDA's control of drug experimentation on humans and changed the way new drugs were regulated.

Under the 1938 law, drug manufacturers had only to show that their drugs were safe. Under the 1962 law, for the first time, they also had to show that all new drugs were effective. Kelsey was there for both of them. She participated in the creation of two of the most important public health laws in the nation's history, simply as a scientist trying to understand what had happened and how the public health could be protected.

The 1962 amendments required informed consent from patients used in drug studies, and sponsoring drug companies were required to report to FDA any adverse reactions to the drug. FDA made Kelsey head of its investigational drug branch, created to evaluate and monitor clinical trials for compliance with these new drug regulations. FDA grew along with its increased regulatory responsibilities. In 1960, Kelsey was one of only seven full-time and four young part-time physicians reviewing drugs, today there are nearly 400 medical officers at the FDA.

Thalidomide Today

Thalidomide never disappeared. Since the discovery in the 1960s of its ability to cause birth defects, the drug has continued to be studied throughout the world to treat cancer and other life-threatening or disabling conditions. FDA approved the drug for the first time in this country in 1998 under the brand name Thalomid, manufactured by Celgene Corporation. It was approved for one condition only: erythema nodosum leprosum (ENL), a severe and debilitating complication of leprosy. Because of the dangers the drug still presents to the unborn, FDA took unprecedented regulatory steps to control Thalomid's marketing. Thalidomide continues to be evaluated in similarly controlled FDA-approved studies. The drug inhibits the growth of new blood vessels in tumors, and has shown the most promise in treating multiple myeloma (a cancer of the bone marrow) and Kaposi's sarcoma (an AIDS-related cancer). Thalidomide has also shown potential to treat solid tumors in the prostate and brain, as well as graft-versus-host disease, a complication of bone marrow transplants.

Kelsey knows that thalidomide can give relief to patients with leprosy and perhaps other diseases, but is concerned about its widespread use--particularly with the availability of Internet sales. "We need to take precautions," she says, "because people forget very soon."