

## *Virtual Mentor*

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### **VIEWPOINT**

#### **Commemorative Issue: Protecting the Public: Dr. Frances Oldham Kelsey**

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*President John F. Kennedy, in August 1962, awarding Dr. Frances Oldham Kelsey the President's Medal for Distinguished Federal Civilian Service for her exceptional judgment in evaluating the drug Thalidomide. Dr. Kelsey was only the second woman to receive this award—the highest honor that can be bestowed upon a US civilian.*

That Dr. Frances Oldham Kelsey saved countless lives and prevented numerous physical deformities of infants and children is a remarkable accomplishment in any career. More remarkable still is the fact that she accomplished this feat not through the discovery of a cure, the development of an innovative surgical procedure, or the invention of a life-saving device. Rather, it was Dr. Kelsey's professional behavior—her unwillingness to compromise the priorities of patient health and safety—that single-handedly averted an appalling tragedy nearly thrust upon an unsuspecting American public.

In September 1960, Dr. Kelsey was a newly appointed member of the Food and Drug Administration (FDA). Her very first assignment was to review the application for the drug Kevadon. Synthesized in 1954 and introduced to the market on October 1, 1957 in West Germany, the drug—known there by the name Thalidomide—was hailed as a wonder cure for insomnia<sup>1</sup>. Non-addictive and non-toxic, Thalidomide induced sleep and was prescribed as a sedative that promised no side effects. As its popularity grew, it soon became the drug of choice prescribed to pregnant women combating symptoms associated with morning sickness. By 1960, Thalidomide was popularly prescribed throughout the world, including Europe and Canada.

The application by the Richardson-Merrell pharmaceutical company of Cincinnati to introduce Thalidomide under the brand name Kevadon to the US market reached the desk of Dr. Kelsey less than 1 month after her appointment to the FDA. Richardson-Merrell expected a routine approval for the drug. To Dr. Kelsey, the evaluation process for which she was responsible was anything but routine. Alarmed by the paucity of clinical evidence to support the drug's safety claims, she rejected the application with the request for more clinical evidence of its safety.

Of particular concern to Dr. Kelsey and her staff was one of the drug's major selling points: unlike barbiturates, which induced sleep but also induced death if taken in

large quantities, Thalidomide could be ingested in large quantities, seemingly without toxic side effects. However, Dr. Kelsey recalled a study she conducted on rabbits as a young post-doctoral pharmacologist at the University of Chicago in 1942. As a member of a team seeking to create a synthetic cure for malaria, Dr. Kelsey had noted that, although adult rabbits metabolized quinine rapidly, pregnant rabbits were less able to metabolize the drug and embryonic rabbits had no ability to metabolize the drug. Furthermore, Dr. Kelsey noted that the drug did indeed pass through the placental barrier between mother and developing fetus. Recalling those observations in reviewing the Thalidomide application, Dr. Kelsey was concerned that physiological changes such as pregnancy might change the absorption of Thalidomide, leading to harmful consequences<sup>2</sup>.

Responding to Dr. Kelsey's requests for more clinical proof of the drug's safety, Richardson-Merrell submitted additional evidence, but she again rejected the application on the grounds that the reports were testimonial—not clinical—in nature. As autumn closed in on the Christmas holiday season—the most lucrative time of the year for the sale of sedatives—the pharmaceutical company, frustrated by the repeated—and in their view, unnecessary—delays, began to pressure Dr. Kelsey with visits and phone calls to her superiors. Despite the increasing pressure, Dr. Kelsey remained steadfast in her demand for thorough clinical studies demonstrating the drug's safety.

In December 1960, Dr. Kelsey read a letter published by the *British Medical Journal*<sup>3</sup> that strengthened her skepticism regarding the safety claims of the drug. The letter was from a physician whose patients had taken Thalidomide over long periods of time and were now experiencing pain in their extremities. Concerned that this report was the first indication of toxicity effects, Dr. Kelsey continued to refuse to grant permission for marketing the drug in the US.

In the meantime, physicians throughout the world were beginning to report an unusual increase in births of severely deformed infants, particularly of infants born with the unusual condition of phocomelia. Although the first known casualty of Thalidomide—a child with severely deformed ears—was born on December 25, 1956, well before the mass marketing of the drug, the medical community was slow to recognize the link between Thalidomide and birth defects<sup>4</sup>. It was not until November 1961 that a German pediatrician determined that 50 percent of mothers with deformed children had ingested Thalidomide in the first trimester of pregnancy. German health authorities pulled the drug from the market, and other countries followed its lead<sup>4</sup>. Faced with growing evidence against the use of Thalidomide, Richardson-Merrell Pharmaceutical company withdrew its application from the FDA in March 1962<sup>5</sup>.

In the few years that the drug was on the world market, thousands of children were born with Thalidomide-related deformities<sup>6</sup>. Many did not survive their first year. Countless more miscarriages were traced to the use of Thalidomide. The damage in the United States, due to the work of Dr. Kelsey, was small by comparison, with 17

children documented to have Thalidomide-associated deformities. These children were affected during clinical trials of the drug, prior to its approval. During this investigational period, Richardson-Merrell distributed more than 2.5 million Thalidomide tablets to more than 1,000 doctors who, in turn, gave the tablets to nearly 20,000 patients—several hundred of whom were pregnant women.

By refusing to compromise her exacting standards for patient safety, Dr. Frances Oldham Kelsey prevented what could have been a tragic outcome for thousands of children in the US. For her vigilance Dr. Kelsey received the highest honor that can be bestowed upon a US civilian: the medal for Distinguished Federal Civilian Service, presented to her by President John F. Kennedy, on Aug. 17, 1962. Dr. Frances Oldham Kelsey's commitment to the primacy of patient health and safety serves as a model of professional behavior for all physicians.

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