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By Kaylee J. Rice

The mid-twentieth century was a uniquely optimistic time. Both world wars were over, and nations across the globe were starting to gain their footing once again. Nuclear technology had created a new terror, but seemingly boundless new potential as well. Just a few decades prior, the discovery of penicillin and subsequent related antibiotics had greatly reduced the number of people who died of bacterial diseases. The rest of the medical world followed suit, with new "wonder drugs" entering the market every day, promising to fix every imaginable ailment. However, one of these drugs would be remembered not for the suffering it alleviated, but for the devastation it caused: thalidomide. Ultimately, the thalidomide tragedy forced the United States to realize that, although they had narrowly averted disaster this time, in the future they would not be so lucky unless they created stricter regulations for drugs.

First, however, it is necessary to understand the history of thalidomide itself. Thalidomide was first synthesized by a Swedish drug company in 1954 as a tranquilizer. When they tested it on lab animals, though, the drug did not appear to have a sedative effect, and so they discarded it and started over.[1] That same year, a company in West Germany called Chemie Grunenthal picked it up, hoping to market it as an anti-convulsant for epileptics. However, they discovered that, while thalidomide made a poor anti-convulsant, it had a sedative effect on humans that it did not have on lab animals.[2] By 1960, Grunenthal was selling thalidomide under the name Contergan, and its popularity took off. Helen Taussig, author for *Scientific American*, writes that Contergan was used for almost anything, most notably as an anti-emetic for morning

[1] Helen B. Taussig, "The Thalidomide Syndrome," *Scientific American* 207, no. 3 (August 1962): 30.

[2] Ibid.

sickness and as a tranquilizer to help pregnant women get a good night's sleep.[2] Its popularity came largely because of its reputation as a "safe" tranquilizer—unlike barbiturates, another popular sedative at the time, doctors in the 1950s and 60s thought that the body did not absorb thalidomide, meaning it did not carry the risk of accidental overdose or of being used as a means of suicide, like barbiturates did.[3] Advertisements for Contergan and other thalidomide-based drugs boasted that it was "non-toxic" and had "no known toxicity."[4]

But was this "wonder drug" really as harmless as the drug manufacturers liked to claim? The first indication that something was not right came during the fall and winter of 1960-1961, when long-time thalidomide users started to report symptoms of polyneuritis: specifically, of tingling hands and thumb atrophy.[5] Alarmingly, these symptoms could take a long time to go away. One doctor, Dr. J.A. Simpson from Edinburgh, wrote to *The British Medical Journal* to state that his patients who experienced polyneuritis due to Thalidomide at the time of his original letter (published January 28, 1961) were still experiencing symptoms in November, ten months later.[6] By April, 1961, these reports were numerous enough that West Germany made Contergan available by prescription only (it had formerly been an over-the-counter drug in West Germany, although a prescription was required in all other

[2] Ibid.

[3] Linda Bren, "Frances Oldham Kelsey," *FDA Consumer* 35, no. 2 (March/April 2001): 24.

[4] "Simple Thalidomide Historical Timeline," The Thalidomide Society, accessed December 1, 2018, https://www.thalidomidesociety.org/thalidomide-timeline/.

[5] Taussig, "The Thalidomide Syndrome," 30.

[6] Eric C.O. Jewesbury, Denis Burley, J.A. Simpson, T.N. Rudd, and R.N. Greenhalgh, "Neuropathy After Thalidomide ('Distaval')," *The British Medical Journal* 2, no. 5262 (Nov. 1961): 1286.

countries where it was for sale).[7] Aside from this seemingly minor complaint, thalidomide was considered to be completely safe.

Unfortunately for thousands of families, peripheral neuritis would soon take the backseat to a much more severe and dramatic side effect. As the spring of 1961 turned into summer, doctors all over Germany began to notice a disturbing trend: more and more babies were being born with a condition called *phocomelia*, a deformity involving shortening of the long bones of the arms and legs, often creating the appearance that the patient's hands and feet are attached directly to their shoulders or hips. Typically, phocomelia is very rare—there were only 12 recorded cases in West Germany in all of 1959. In contrast, by the middle of the summer of 1961, hundreds of babies across Germany had been born with this condition.[8] Doctors everywhere were scrambling to track down some sort of cause for this sudden outbreak. Two German physicians, W. Kosenow and R.A. Pfeiffer, frantically studied the affected babies to see if they could find a common genetic factor, but they could not. Ultimately, they decided that the problem was caused by the babies' mothers being exposed to a teratogen between the third and sixth weeks of pregnancy, when the arm and leg buds of the fetus are just beginning to form.[9] Even with this discovery, Kusenow and Pfeiffer were unable to identify exactly what the teratogen was. A wide variety of possibilities were suggested, including nuclear fallout.[10]

Meanwhile, another German doctor, Widukind Lenz, was sending out lengthy questionnaires to the parents of affected babies, asking about any possible cause he could think of. At first, there seemed to be no common factor. However, when 20% of the patients he surveyed reported taking Contergan during their pregnancy, Lenz

[7] Taussig, "The Thalidomide Syndrome," 30.
[8] Taussig, "The Thalidomide Syndrome," 29.
[9] Ibid., 30.
[10] Ibid.

realized that he might have found the mysterious teratogen.[11] He sent out another questionnaire asking specifically about Contergan usage, and this time 50% of his patients could confirm without a doubt that they had taken Contergan; apparently, the drug was considered to be so harmless that they hadn't even thought of mentioning it on the first survey.[12]

Having found a strong association between Contergan and the sudden phocomelia outbreak, Lenz took immediate action. On November 15, 1961, he warned Chemie Grunenthal about the correlation between thalidomide and infant deformities, recommending that they take it off the market immediately.[13] On November 20, at the annual pediatricians' meeting in Dusseldorf, Germany, Lenz announced that he had discovered an association between a popular drug and the increased incidence of phocomelia, although he did not name the drug specifically. However, by the end of the meeting, so many physicians had approached him to ask if he was talking about Contergan that it was generally known which drug he meant.[14]

Other doctors were slowly but surely coming to the same realization. On November 27, 1961, an Australian physician, W.G. McBride, alerted the Australian branch of the British company Distiller's Limited that their version of a thalidomide-containing drug (called Distaval in the U.K.) was associated with birth defects.[15] McBride also published an article containing his findings in the medical journal *The Lancet*, sparking discussion about the drug across the worldwide medical

[11] Ibid., 31.

[12] Ibid.

[13] Taussig, "The Thalidomide Syndrome," 31.

[14] Ibid., 31.

[15] Ibid.

community.[16] One day after McBride alerted Distillers Limited of his findings, Chemie Grunenthal officially removed Contergan from sale in Germany.[17]

For thousands of families, though, this action came too late. Thalidomide had spread to dozens of different countries under a variety of names—Contergan in Germany; Distaval in Britain, Australia, and New Zealand; Softenon in Portugal; Talimol in Canada; and Kevadon in the United States.[18] Overall, more than 10,000 children in 46 different countries were born with birth defects resulting from thalidomide, a condition which would soon come to be known as "the thalidomide syndrome".[19]

The thalidomide syndrome varied in its intensity. The most notable symptom was phocomelia, especially of the arms, with the radius, ulna, and occasionally the humerus being entirely absent.[20] Classic phocomelia cases typically affected only one arm, but in cases brought on by thalidomide, the damage was nearly always bilateral, affecting both arms and sometimes the legs as well. If the legs were affected, deformities of the pelvis and femur often caused the feet to splay outward as well.[21] Other common symptoms included flattened noses, facial paralysis, internal deformities, and *hemangomia*, or "strawberry-marks" on the face (although these were usually temporary and harmless).[22] Thankfully, despite these severe physical defects,

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[16] "Simple Thalidomide Historical Timeline," The Thalidomide Society, accessed December 1, 2018, https://www.thalidomidesociety.org/thalidomide-timeline/.

[17] Taussig, "The Thalidomide Syndrome," 31.

[18] Ibid., 30.

[19] Nancy Kriplen, "The Heroine of the FDA," *Discover* 38, no. 2 (March 2017).

[20] Taussig, "The Thalidomide Syndrome," 30.

[21] Ibid.

[22] Ibid.

"thalidomide babies," as they came to be known, were almost always of normal intelligence.[23] One-third had such severe deformities that they died soon after birth, but the two-thirds of thalidomide babies who survived had normal life expectancy.[24]

Most baffling to doctors, though, was the seeming lack of association between the amount of thalidomide taken by the mother and the severity of the child's condition. Taussig, writing during the crisis, states that, "there is apparently no relation between the amount of the drug ingested and the severity of the malformation. A single dose of 100 milligrams appears to be enough to cause severe phocomelia, yet in other instances the same doses may produce only a mild abnormality."[25] Eventually, Lenz came to the realization that this was because of the limited time in which thalidomide affected the fetus: deformities would only occur if thalidomide was taken between the 38th and 42nd day of pregnancy.[26] Therefore, large amounts of thalidomide taken earlier or later than this limited window would not cause birth defects, while small amounts taken during this time could result in a severe case of thalidomide syndrome.

However, one major world power had remarkably few thalidomide babies: compared to hundreds or thousands of thalidomide babies born in other countries where thalidomide was for sale, the United States had only 17 confirmed cases of thalidomide syndrome.[27] It would be easy to assume that this was because the United States had the most stringent drug regulation laws, but this wasn't true. The real reason that the United States managed to avoid a large-scale thalidomide tragedy was the tireless work of one woman: Dr. Frances Oldham Kelsey.

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[23] Ibid.
[24] Ibid.
[25] Ibid., 32.
[26] Ibid., 32.
[27] Taussig, "The Thalidomide Syndrome," 30.

Kelsey was born on Vancouver Island, Canada, in 1914. She was schooled in both Canada and England, showing a strong inclination toward the sciences from an early age, eventually going on to earn her PhD in pharmacology from the University of Chicago in 1938.[28] As a woman in the medical field, she had to deal with many difficulties as her career advanced. For example, when she applied to the University of Chicago's doctorate program (and, simultaneously, for a position as a research assistant), Dr. Geiling, the program director, addressed her acceptance letter to "Mr. Oldham." Rather than correcting him, Kelsey decided to show up and let him discover his mistake for himself.[29]

During her time at the University of Chicago, Kelsey and Geiling participated in a research program that sought to find a synthetic version of quinine, an anti-malarial drug. Although they never accomplished this goal, Kelsey made an interesting discovery: pregnant rabbits were significantly less able to process quinine than normal rabbits, and embryonic rabbits were unable to process it at all.[30] Unbeknownst to Kelsey (or anyone else, for that matter) was the way that this discovery would later inform the most notable accomplishment of her career: keeping thalidomide from being sold commercially in the United States.

After graduating from the University of Chicago, Kelsey worked for the *Journal of the American Medical Association* (or JAMA for short) as an editorial assistant. Her job was to confirm the scientific accuracy of articles submitted to the journal for publication.[31] This led to a job as a medical examiner at the FDA. Specifically, Kelsey worked for the branch of the FDA that regulated and approved new drugs. Once an

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[28] Kriplen, "The Heroine of the FDA."

[29] Leila McNeill, "The Woman Who Stood Between America and a Generation of 'Thalidomide Babies': How the United States Escaped a National Tragedy in the 1960s," *Smithsonian Magazine*, May 8, 2017.

[30] Bren, "Frances Oldham Kelsey," 24.

[31] Nancy Kriplen, "The Heroine of the FDA," *Discover* 38, no. 2 (March 2017).

NDA (New Drug Application) was submitted for approval, three people—a chemist, a pharmacologist, and a medical officer. As the medical officer in this process, Kelsey's job was to determine whether the studies submitted to prove the drug's safety were valid or not.[32] Kelsey's first project in this position came to her desk in September, 1960. It was an application for the sale of a thalidomide-containing drug called Kevadon, which the William S. Merrell company was hoping to market in the United States. The FDA gave this to Kelsey as her first job because they thought it would be an easy approval, given the popularity other thalidomide-containing drugs already enjoyed in other countries.[33] Looking back, Kelsey would later comment, "As it turned out, it wasn't all that easy."[34]

In the 1950s and 60s, the process for approving a new drug was heavily skewed in favor of the drug companies. First of all, the FDA could only regulate the safety of a drug, not its efficacy.[35] Therefore, a drug with no ill effects that did absolutely nothing could claim to be the cure for all sorts of ills, and there was nothing the FDA could do. Additionally, if no objections were raised against the new drug, it would be automatically approved for sale after 60 days, even if no one had technically approved it.[36] Because of this, most drugs were approved as long as there were no glaringly obvious side effects. However, this was not to be the case with Kevadon.

In looking at the Merrell company's submission, several red flags appeared to Kelsey. First of all, the clinical studies designed to

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[32] Ibid.

[33] Robert D. McFadden, "Frances Oldham Kelsey, Who Saved U.S. Babies from Thalidomide, Dies at 101," *The New York Times*, August 7, 2015.

[34] Bren, "Frances Oldham Kelsey," 24.

[35] "Government Actions in Times of Crisis: Lessons from the History of Drug Regulation," *Journal of Social History* 18, no. 3 (Spring 1985): 5-6.

[36] Ibid., 5.

prove the drug's safety were incomplete. Second (and possibly more concerning), Kelsey realized that "many of the submissions from doctors (she recognized a few of the names from questionable JAMA papers) read more like advertising testimonials than well-designed, well-executed scientific studies."[37] Because of these flaws, she returned the submission to the Merrell Company, asking for more information before she could approve the drug. Meanwhile, she decided to do some extra reading on thalidomide to see what other medical professionals were saying about the drug. To her surprise, she read in the *British Medical Journal* that with long-term use, it was found to cause peripheral neuritis—a side effect that William Merrell had not seen as relevant enough to mention in the submission.[38] This side effect instantly led Kelsey to be suspicious of Kevadon. As she put it, "the peripheral neuritis did not seem the sort of side effect that should come from a simple sleeping pill."[39] When she addressed the Merrell Company with this concern, Merrell replied that at least Kevadon was "safer than barbiturates."[40]

From that point on, Kelsey and the Merrell Company were engaged in an openly antagonistic relationship, with Merrell Company representatives badgering Kelsey daily, trying to get her to approve Kevadon, and Kelsey doggedly refusing their application every 60 days.[41] Merrell told Kelsey forthright that they wanted to get the drug on the market before Christmas, "Because that's when our best sales are."[42] As she kept refusing to approve Kevadon, Kelsey also continued to

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[37] Kriplen, "The Heroine of the FDA."

[38] Ibid.

[39] McNeill, "The Woman Who Stood Between America and a Generation of 'Thalidomide Babies': How the United States Escaped a National Tragedy in the 1960s."

[40] Ibid.

[41] "Government Actions in Times of Crisis: Lessons from the History of Drug Regulation," 5.

[42] Bren, "Frances Oldham Kelsey," 24.

research its possible effects. Because of her former research on the effects of quinine on embryonic rabbits, she began to wonder if thalidomide too was metabolized differently by mothers and their unborn children. Could it possibly be harmless to adults, but damaging to fetuses?[43]

This war went on for over a year, both sides fighting their battles 60 days at a time. The Merrell Company continued to renew their application through November, 1961, when the first links between thalidomide and fetal abnormalities came to light; however, by April, 1962, they knew they had been beaten and withdrew their application for good.[44] In total, there were 17 thalidomide babies born in the United States—partially from citizens who had obtained Distaval or Contergan abroad and partially from the 2.5 million thalidomide tablets that the Merrell Company had distributed on "an investigational basis."[45] The end result was a tragedy, certainly for those families, but the overall sense in the United States was that a disaster had been narrowly averted. Lawmakers seemed to realize how close they had come to catastrophe. In October, 1962, the Kefauver-Harris amendment passed, leading to stricter FDA regulations on new drugs, as well as regulations about informed consent for those who took experimental drugs on a trial basis.[46] Dr. Frances Oldham Kelsey was awarded the President's Award for Distinguished Civilian Service, becoming only the second woman

[43] Ibid.

[44] McNeill, "The Woman Who Stood Between America and a Generation of 'Thalidomide Babies': How the United States Escaped a National Tragedy in the 1960s."

[45] Bren, "Frances Oldham Kelsey," 24.

[46] "Government Actions in Times of Crisis: Lessons from the History of Drug Regulation," 5.

ever to receive this honor.[47] A year later, she was promoted to the position of Chief of the Investigational Drug Branch of the FDA; four years after that, she became the Director of the Office of Scientific Investigation, a position which she held for 40 more years.[48]

The thalidomide tragedy was a sobering check on the unfettered progress that had marked the medical field ever since the turn of the century. Soon after 1962, it faded into the background once again, but for the victims and their families, life would never be the same again. The rest of the world had changed too, albeit in a less dramatic way. Instead of looking at drugs as miracles, people became suspicious and began to wonder exactly what their doctor was prescribing them. Certainly, life had changed forever for drug companies and the FDA—following the thalidomide tragedy, drug regulations became stricter than ever before in an effort to prevent such a disaster from ever happening again. Ultimately, a drug that had once been hailed as a cure-all became synonymous with misinformation and distrust. Although the United States narrowly avoided a full-scale thalidomide tragedy, its drug regulation policies would always carry the shadow of thalidomide.

[47] McNeill, "The Woman Who Stood Between America and a Generation of 'Thalidomide Babies': How the United States Escaped a National Tragedy in the 1960s."

[48] Ibid.