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Thalidomide: The Tragedy of Chiral Chemistry

Billy Joel's famous song "We Didn't Start the Fire" recounts notable events from the last half of the 20th century. The tenth verse ends with the phrase "Children of Thalidomide," referring to one of the greatest tragedies of modern medicine, when a drug called Thalidomide was marketed to pregnant women to relieve morning sickness. It was discovered only later that thalidomide is a teratogen, something that causes birth defects in unborn infants. Thalidomide illustrates how chemical technology in the pharmaceutical industry can fail, and the disastrous consequences that occur as a result. This tragedy had a tremendous global impact on medicine, pharmacology, and society; its legacy still resonates today.

The thalidomide story began in West Germany, where the drug was first synthesized in 1954 (Stephens 8). The pharmaceutical company Chemie Grünenthal found that thalidomide was non-lethal in animals even at extremely high doses, and that in humans it produced a "soothing, calming, sleep-inducing effect on patients" (9, 13). Best of all, it seemed to have no side-effects (Teff 1). Grünenthal began selling thalidomide in 1957 as an over-the-counter sedative, propelled by an aggressive marketing campaign that highlighted how safe (non-toxic) it was (Stephens 14, 15). Thalidomide was a hit, and by 1961 the drug was outselling its nearest competitor by a factor of five (15). Before long, thalidomide was sold in forty-six countries throughout Europe, Asia, Africa, and the Americas under at least thirty-seven different brand names (16). As sales increased, so did reports of side effects.

Complaints began to arrive at Grünenthal from patients who reported feeling numbness and tingling in their hands and feet (20). Doctors inquired whether thalidomide caused polyneuritis, a type of severe nerve damage (Knightly 32). Grünenthal denied all claims and

resisted pressure to put thalidomide under prescription; most of their revenue came from over-the-counter sales (Stephens 22, 25). The company continued to sell and promote thalidomide and suppressed all information about the complaints they were receiving (21, 22). Meanwhile, a curious phenomenon had begun to appear in European hospitals.

"Phocomelia" (literally 'seal flipper') is an extremely rare birth defect that affects on average one out of four million births, but in the late 1950s this condition suddenly became alarmingly prevalent (21). Infants were born with grotesque deformities – some were missing entire limbs, while others had hands or feet that were directly attached to their torso. Others were born with deformed ears, eyes, genitals, or internal organs (Hawthorne 43). In 1961 alone, hospitals in Hamburg, Germany saw eight babies born with phocomelia, out of 6,420 births (Stephens 30). At first, physicians were baffled by this bizarre outbreak; phocomelia was such a rare condition that many had never heard of it (21). Doctors turned into investigators, and it gradually became clear that the only link between the mothers of these deformed babies was that they had taken thalidomide during their pregnancy. Aside from being marketed as a sedative, thalidomide had also been promoted for providing relief from morning sickness (Hawthorne 43).

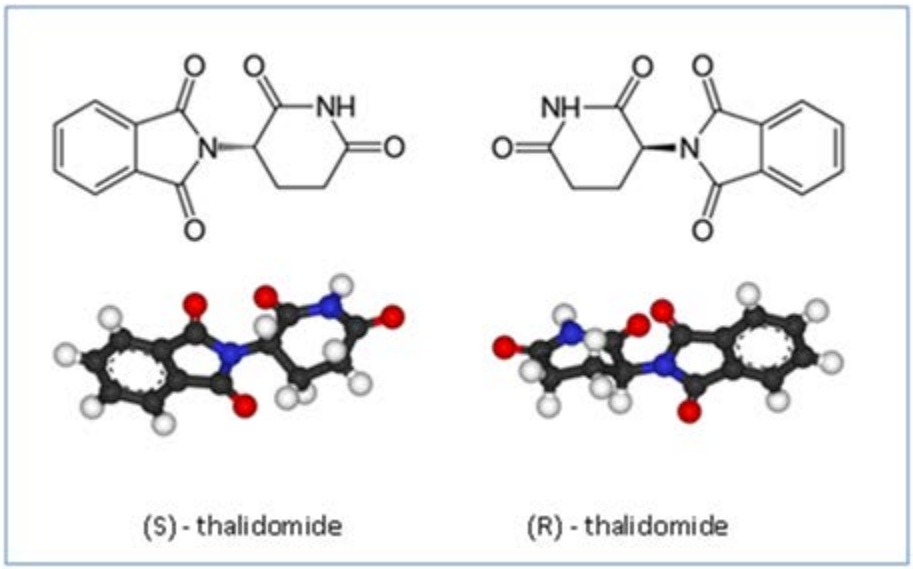
As negative press increased, Grünenthal finally put thalidomide under prescription in the summer of 1961 and in November it reluctantly pulled the drug from the German market (Stephens 29, 34). The British and Australian distributors of thalidomide soon followed, but it took months before the drug disappeared altogether, especially in poorer areas like South America (36, 67). It is estimated that in all, 8,000 – 12,000 infants were deformed by thalidomide; 5,000 of them survived into adulthood (37).

Even before scientists understood how thalidomide caused birth defects, it was clear that Chemie Grünenthal had not followed the scientific method in testing the drug. Other pharmaceutical companies had studied and rejected thalidomide because it had no noticeable effects on animals, even at high doses (8, 9). One researcher at Grünenthal was interested in how the structure of thalidomide was similar to that of known barbiturates, which led the company to test the drug as a human sedative; thalidomide proved to be extremely successful (Knightly 15). A small number of patients exhibited side effects such as rashes, shivering, and buzzing in the ears, but they were so few that they were deemed insignificant by the company (Stephens 14). In addition to drug tests, Grünenthal also handed out hundreds of thalidomide pills to doctors with little monitoring or follow up (10). Ironically, the first thalidomide victim was a baby girl born to an employee of the company (19).

Thalidomide was never approved by any regulating body such as the FDA – at the time West Germany had none (Grünenthal). Oversight of the pharmaceutical industry was largely of self-monitoring. Nonetheless, to gain support for their drug from the pharmaceutical community and from distributors overseas, Grünenthal needed to prove that thalidomide affected animals as well (Stephens 14). To do this, researchers devised a 'jiggle cage,' to prove that thalidomide also worked as a sedative on lab rats (14). This device is a prime example of what some call 'voodoo science,' but it was convincing enough for thalidomide to gain acceptance. No attempt was made to discover how thalidomide is metabolized in the body, and it was never tested on primates or pregnant animals (Knightly 23, Teff 2).

It was not until many years later that scientists began fully to understand why thalidomide is a teratogen; their discoveries highlighted the importance of basic chemistry in drug synthesis. The chemical formula of thalidomide is $C_{13}H_{10}N_2O_4$, but, because one of the carbon atoms is

chiral, thalidomide has two different forms, or enantiomers [Fig. 1] (Cotton 116). Although the (R)- and (S)- enantiomers consist of the same elements, they have drastically different effects on the body. While both act as sedatives, the (S)-enantiomer is also a teratogen because it inhibits angiogenesis, the formation of new blood vessels (116). Under normal conditions in the womb, integrin proteins[1] attach to blood-vessel receptors and cause a cascade of reactions that result in the formation of new blood vessels (116). However, (S)-thalidomide resembles DNA such that it



can interfere with the synthesis of integrin proteins, stunting blood-vessel growth, resulting in severely deformed or non-existent limbs, organs, and facial features (116). Thalidomide is also metabolized differently by different animals, which is why companies that tested thalidomide found it had no noticeable effect on lab animals (Stephens 14).

It is impossible to say how much Chemie Grünenthal knew about the different enantiomers of thalidomide because most of the documentation of their research was destroyed or 'misplaced' (Stephens 12). However, because chirality had been discovered many years earlier by Louis Pasteur, it is more likely that Grünenthal ignored the implications of this

[1] Integrins are a general category of cell surface-receptors that participate in cell-cell signaling, cell adhesion, and gene expression (Liu 1).

discovery: because chiral molecules exist, curing a disease may require a particular chiral molecule (Kean 181).

Prior to 1968, separating chiral enantiomers of a molecule required exploiting a difference in their physical properties, for example crystallization point or solubility (174, 182), assuming that there is a difference. However, the Thalidomide isomers have none (Cotton 116). Yet even if Grünenthal had isolated the benign isomer of the drug, birth defects would still have occurred. Thalidomide has the ability to racemize inside the body, meaning that one enantiomer can convert spontaneously into the other (Cotton 116). Administering a pure sample of (R)-thalidomide to patients would not protect them from the damaging effects of the (S)-isomer.

The thalidomide disaster had an immediate and long-lasting impact on society. First and foremost, it left a terrible scar on the thalidomide victims and their families, who had to deal with - and are still dealing with – the consequences. Many countries adopted stricter regulations on drug testing. In the United States, thalidomide spurred the passage of the Kefauver-Harris Amendments to the 1938 Food and Drug Act. These amendments mandated stricter standards for testing and marketing pharmaceutical products (Hawthorne 44). America had escaped the thalidomide tragedy thanks to the courage of a young reviewer at the FDA who resisted pressure to approve the drug; these new amendments codified her cautious attitude into law (44).

Thalidomide also sparked numerous ethical debates. It gave new-found strength to the abortion debate in many countries when some women, who realized they had taken thalidomide during their pregnancy, campaigned for a chance to abort their fetus (Stephens 70). Thalidomide also set new precedents for class-action lawsuits and compensation for victims of pharmaceutical malfeasance. It also spurred debates on moral justice, freedom of the press, and the relationship between government and industry. In the United Kingdom, the government had refused to launch

a public inquiry and had leaned heavily on the press to abstain from any mention of the drug (81). Distillers, the British distributor of thalidomide, was one of the country's largest corporations and it held enormous influence in many levels of the British government (82).

The thalidomide disaster also had a significant impact on the pharmaceutical industry. The medical profession was thrown into a state of shock, and drug companies were terrified of the consequences that thalidomide had caused for Chemie Grünenthal and for other distributors of the drug (Knightly 117). Most companies were willing to obey the new stricter standards of drug testing set by governments. It became regular practice for drug companies to test their products on pregnant animals and primates, and they provided new funds for research on chiral drugs (Stephens 13, Knightly 20). As a result, in 1968 the scientist William Knowles devised a method of 'asymmetric chiral synthesis' as a way to efficiently separate chiral molecules (Kean 181). He discovered how to use a rhodium catalyst to force molecules to 'inflate' into the proper enantiomer form, a feat that won him the Nobel prize in 2001 (Kean 181, nobelprize.org).

There is one small silver lining to the thalidomide story. Beginning in the 1970s, the drug was discovered to have life-saving benefits for victims of leprosy, HIV, and certain other diseases (Cotton 117, Stephens 135). For this reason, thalidomide is still in use today, although its production is strictly controlled and its use strictly monitored through the STEPS program (System for Thalidomide Education and Prescribing Safety). Women who are or may become pregnant are prohibited from taking it (Stephens 157). Despite the benefits of thalidomide, and the controls on its distribution, there remain ongoing debates about the ethics of its use.

The thalidomide tragedy could have been avoided were it not for the unethical and unscientific practices of Chemie Grünenthal and other distributors of the drug. Their shoddy methods of drug testing and disregard for the implications of chiral chemistry led to disastrous

consequences for innocent people. Thalidomide led to the adoption of more rigorous standards in the pharmaceutical industry and it sparked many ethical debates about medicine that still resonate today. It is perhaps the best example of how tiny structural differences between molecules must never be ignored. Chemie Grünenthal survived as a company although it has been involved in many lawsuits with thalidomide victims – including some that are still ongoing. It was not until August 2012 that Grünenthal apologized for their role in the thalidomide tragedy, but to many people alive today who are still living with terrible deformities, it seemed too little and much too late (Jordans).

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