The Thalidomide Tragedy

The curtains are open, allowing the soft glow of warm sunlight to fill the otherwise sterile hospital room. You hear the muffled scuffling of leather shoes on the vinyl tile through the door in the hall. You are tracing the outline of your swollen belly with your fingers, and excitement fills you. You can't wait until the moment you get to hold your happy, healthy baby girl for the first time.

The doctor enters and starts to babble off a list of instructions to the midwife. It all went by like a blur, one moment you were being told to push and the next – a high pitched wail rang through the room. A cry you'd imagined so many times, the cry of a healthy baby, the cry of *your* baby! Only, the doctor didn't look so pleased, as he held your baby towards you, you could see it too. You felt a sharp pain in your heart and your eyes welt up with warm tears. She had no true arms or legs, only short nubs left in their place. The doctor placed the limbless infant with the midwife and softly asked you, "What were you prescribed to treat for morning sickness, again?" you answered, "Distaval. Why, Doctor?". You watch a wave of anguish wash over the doctors face, and without another word he excused himself quickly, leaving the delivery room with haste.

The doctor's steps echoed down the hallway as he huried towards his office. In the small dimly lit room, he reluctantly added another pale yellow manilla envelope to the ever growing stack on his desk. The note taped to the stack read "Thalidomide & Congenital Abnormalities". This is it, he decides. It has to stop. He moves his chair to the left, adjusting himself in his large L-shape desk. He begins to type, his fingertips sliding swiftly across each cold metal letter on his typewritter. He writes to the highly esteemed medical journal, The Lancet, the following:

> SIR- Congenital abnormalities are present in approximately 1.5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ('Distaval') during pregnancy, as an antiemetic or as a sedative, to be almost 20%... [1]
>
> Dr. William McBride, 1961

In December of 1961, Dr. William McBride published a paper titled "Thalidomide & Congenital Abnormalities" to the Lancet. Like seasoned detectives piecing together a horriffic puzzle, Dr. McBride and his midwife discovered that each of the mothers of the malformed children had one connection, they had all taken the drug thalidomide, commonly marketed in Australia as Distaval, for their morning sickness or as a sleep aide [2].

The first published paper containing research related to thalidomide was published in 1956 by Kunz, Keller, and Mückter from Germany [2]. Their testing on rats revealed that thalidomide did not cause an initial agitation period unlike other sedative drugs of the time, had a more rapid ontake with longer duration, and was virtually non-lethal, even in high doses [2]. Thalidomide suddenly become a beacon of hope for the world of sedatives, sparking excitement and promise among researchers. However, reports to follow were riddled with holes, and offered

misleading conclusions backed by limited data. Reports often failed to compare patients to a placebo group or establish a consistent treatment duration [2]. Despite limited clinical studies, thalidomide was seen as a miracle drug, and launched in Germany in November of 1957 [2], quickly being shoved into the hands of unsuspecting mothers as if it were merely candy.

Thalidomide's reach extended globally, stretching from bustling European cities to the far off shores of Australia, and to the cold lakes of Canada. Just a few short months after its approval in Germany, thalidomide was approved for distribution in the United Kingdom (UK) [3], followed by Japan in 1958 and Norway in 1959 [4]. Notably, thalidomide was never approved for sale in the United States. The Food and Drug Administration (FDA) rejected it due to insufficient research [4]. Their rejection of the drug, however, did not stop pharmaceutical company Richardson-Merrel from putting over 20,000 Americans at risk through clinical trials conducted after thalidomide had already been pulled from pharmacies in Germany [5]. At it's peak, thalidomide had reached 46 countries and was marketed under at least 37 different names. In the UK alone, thalidomide was under the brand names Distaval, Tensival, Valgraine, and Asmaval [6], and was an ingredient in the flu treatment Grippex [7].

Reports began flooding in rapidly: a baby born in Norway with an abnormally short left arm; an infant arriving in Germany with no arms at all; across the Indian Ocean in Australia, another one born with merely nubs in place of all its limbs. Many prominent figures including Dr. McBride argued that thalidomide was the reason behind the sudden large surge of birth defects. Others argued thalidomide could not be the cause, as many mothers claimed to have taken it without any harm to their child, while some mothers of deformed children could not remember taking thalidomide at all during their pregnancy [7]. Later findings would unveil both discrepancies; research would show thalidomide's effect on fetal development is dependent on what stage of pregnancy the drug was taken at, and with thalidomide being marketed under so many different brand names, it's clear why mothers couldn't remember having taken the drug.

It would become apparent that early researchers of the time were so ecstatic to find a more effective, and 'safe' sedative of the time that they forewent testing on pregnant animals. Supported by evidence that even high doses of thalidomide were non-lethal, they took a dangerous leap of faith in marketing the drug as safe for pregnant women, and allowed thalidomide to be sold in pharmacies globally without ensuring its complete safety.

On November 26th, 1961 thalidomide was removed from German pharmacies by the manufacturer. Only a few short days later on December 2nd, the UK manufacturer followed their lead, pulling thalidomide from UK pharmacies [3]. Doctors had been making connections between congenital abnormalities and thalidomide for several years, dating back to December of 1956, when an employee of the German manufacturing company gave birth to a deformed child [3]. Although doctors in all 46 countries were taking note of the increase in deformities throughout the years within their own practices, it wasn't until Dr. McBride's letter to The Lancet that the issue was made public, bringing additional attention to the matter.

It took Dr. McBride just over one month to make his connection to thalidomide. The first baby born with congenital abnormalities delivered by Dr. McBride arrived on May 4th, 1961. The child had obstructed bowels and underdeveloped arms, called phocomelia. This was quite concerning to Dr. McBride, as this was his first case of phocomelia in his career [2]. Only 20 days later, Dr. McBride delivered another child with phocemlia, and then again on June 8th, 1961 [2]. With the weight of responsibility falling heavily on his shoulders, Dr. McBride marched the the Superintendent's office of the Women's Hopsital, and successfully demanded thalidomide be

withdrawn from use at the hospital. Outside of the hospital, however, a different story unfolded. Dr. McBride and his concerns were brushed aside by a Pharmacology Professor at the University of Sydney who remained unconvinced to the harms of thalidomide, and rejected his request to conduct animal testing [2].

The seeds of doubt planted by Dr. McBride took root in the public consciousness after The Lancet paper was published, finally urging manufacturers and pharmacologists to develop additional testing. Their findings, published on April 28th, 1962 revealed thalidomide administered to pregnant rabbits resulted in offspring with shorted front limbs and deformed back limbs [2]. Subsequent testing revealed thalidomide use during pregnancy in animals could result in miscarriages, damage to the eyes, heart, and brain, and limb malformations, depending on which stage of pregnancy thalidomide was administered in [7]. It was discovered thalidomide could bypass the embryonic defense system responsible for preventing toxic substances from entering the embryo, allowing thalidomide to enter embryonic cells and induce stress to the pathways responsible for limb growth [8]. In the wake of this tragedy, many countries set to establish additional safety guidelines regarding the production and sale of drugs, including the UK, Canada, and more. Many began requiring, for the first time, that drugs be tested on pregnant rodents through all stages of pregnancy, and with varying dose levels before being approved for consumption by pregnant women [7].

Though only a mere five years on the market, thalidomide left an permanent mark on the world, leaving a devastating legacy. It is estimated over 10,000 babies were affected by thalidomide worldwide, about half of those babies died before reaching their 1st birthdays [6]. The thalidomide tragedy sparked a wave of legal litigation against the manufacturing companies who sold the drugs, and the American pharmaceutical company, Richardson-Merrel, for their borderline illegal clinical trial. For many, the hope of compensation remained an unfilled promise, as German manufacturer, Chemie Grunenthral, as well as Richardson-Merral were both found not guilty [6][5]. While Chemie Grunenthral and Richardson-Merral found themselves unscathed, the UK manufacturer, Distillers, came to a compensation settlement for UK families, of which they continue to payout [6].

This lesson in history reveals a lot about the nature of science. The thalidomide tragedy follows Karl Popper’s theory of science in which science gathers evidence, not to validate theories but to refute them [9]. Dr. McBride and others worked tirelessly to pull thalidomide from the markets after discovering the theory of thalidomide’s safety was in fact not true. This incident reminds us of the fragility of life and the importance of scientific inquiry and testing in regards to human health and safety.

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