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THE HISTORY OF THALIDOMIDE

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Extract from a lecture given at the 1992 UNITH Congress

As much as possible this document was left in original form, with only occasional punctuation and grammatical corrections. Some clarifications are made in brackets.

Sadly, Dr. Lenz passed away in February 1995.

More than thirty years ago, i.e. in November 1961, I have become involved in the history of thalidomide, and up to the present day I have never lost contact with the problem. It is quite impossible to relate in one lecture (to present) the whole complicated story of the initial synthesis of the drug in 1954, of its marketing in 1957, its spread to many countries in Europe, Asia, Australia, America and Africa, and of the following epidemic of malformations of the limbs and of the ears, often accompanied by malformations of the internal organs. So I decided to restrict my account on the most essential aspects and to tell you more about my personal experience than about the extensive literature on the subject.

Though the first child afflicted by thalidomide damage to the ears was born on December 25, 1956, it took about four and a half years before an Australian gynaecologist, Dr. McBride of Sydney, suspected that thalidomide was the cause of limb and bowel malformations in three children he had seen at Crown Street Women's Hospital. There are only conflicting reports unsubstantiated by documents on the reaction of his colleagues and the Australian representatives of Distillers Company, producers of the British product Distaval between June and December 16, 1961, when a short letter of McBride was published in the Lancet. Distillers Company in Liverpool had received the news from Australia on November 21, 1961, almost exactly at the same time as similar news from Germany.

I had suspected thalidomide to be the cause of an outbreak of limb and ear malformation in Western Germany for the first time on November 11, 1961, and by November 16, I felt sufficiently certain from continuing investigations to warn Chemie Gruenenthal by a phone call. It took ten more days of intensive discussions with representatives of the producer firm, of health authorities, and of experts before the drug was withdrawn, largely due to reports in the press. Dispute on the question, whether thalidomide did or did not cause malformations was going on for months, though independent confirmation of Dr. McBride's and my observations rapidly accumulated. Chemie Gruenenthal continued to deny the ***teratogenic*** effects of thalidomide for years, but there was a growing suspicion that this was not due to honest ignorance but to the purpose of weakening the accusations against the firm.

In some countries, e.g. Belgium, Brazil, Canada, Italy and Japan, thalidomide continued to be sold for several months (after withdrawal of the drug from West German and British markets).

From an increasing number of well documented cases in which the mother had definitely taken thalidomide in early pregnancy it has become possible to delineate the spectrum of malformations attributable to the drug.

These were:

1. Absence of the auricles with deafness.
2. Defects of the muscles of the eye and of the face.
3. Absence or hypoplasia of arms, preferentially affecting the radius and the thumb.
4. Thumbs with three joints.
5. Defects of the femur and of the tibia.
6. Malformations of the heart, the bowel, the uterus, and the gallbladder.

On the other hand, it has been possible to recognize types of limb defects which are certainly not caused by thalidomide. The clear distinction of thalidomide from non-thalidomide cases is important for two reasons, first as a basis for recompensation, second for genetic counselling. Affected individuals and their parents have a right to know, whether there is any recurrence risk for children or brothers and sisters of the patients to have the same malformations. In most cases a careful study of the type of malformations will permit a clear and reliable diagnosis, but some doubtful cases remain. In all definite thalidomide cases, children born later following a pregnancy without thalidomide, did not show similar malformations. The same is true for the children of thalidomide victims. In the recompensation scheme, however, thalidomide damage was also acknowledged in some doubtful cases. So a far (some) children born to mothers or fathers erroneously acknowledged as thalidomide cases, had similar malformations. I have information on 6 such cases born in Belgium, Bolivia, Russia, Western Germany, England and Japan.

Thalidomide may cause quite different malformations in different children. In one case, the ears are missing, there is deafness and paralysis of the muscles of the eyes and the face, but the limbs are normal. In another case, the ears are normal, but the arms are missing. In a third case there are severely shortened arms with only 2 or 3 fingers, often accompanied by internal malformations. In a fourth case, only the thumbs are abnormal with three joints, possibly accompanied by narrowing of the anus. The individual type of thalidomide malformation depends on the time of intake. Thalidomide does not produce malformations if only taken before the 34th day after the last menstruation and usually no malformation if taken only after the 50th day.

Within the sensitive period from day 35 to day 49 there is the following sequence:

1. Absence of ears and deafness: 35th - 37th day
2. Absence of arms: 39th - 41st day
3. Phocomelia with 3 fingers: 43rd - 44th day
4. Thumbs with 3 joints: 46th - 48th day.

If thalidomide has been taken throughout the sensitive period, the consequence may be severe defects of ears, arms and legs and of internal malformations, which often led to early death.

About 40 per cent of thalidomide victims died before their first birthday.

The epidemic of limb and ear malformations followed the sales figures of thalidomide about 8 months later. Thalidomide was withdrawn in Germany by the end of November 1961. An abrupt end of the malformation epidemic was expected by the end of July 1962, and so it happened. In

Japan, where thalidomide was finally withdrawn in September 1962, the peak of the epidemic occurred at a time when the epidemic in Germany had ended. In other countries like Ireland, Italy, the Netherlands, Sweden and the United Kingdom similar parallels between time and amount of thalidomide sales and the consecutive malformation epidemic were found.

The first accusations against Chemie Gruenenthal reached the public prosecutors office at the country court of Aachen by the end of 1961. By 1968 the bill of indictment comprising 972 pages was completed, based on some 500,000 documents. On May 27, 1968, a criminal law suit was started by the public prosecutor against seven men of Chemie Gruenenthal. The case was that they had put on sale a drug which caused an unacceptable degree of bodily harm without having tested it properly, and that they had failed to react to information on side effects in due time, and instead had tried to suppress information. The first 2 1/2 months of the trial were concerned with peripheral neuropathy caused by thalidomide. When I was called as an expert witness on August 12, 1968, I had the opportunity to report my personal experience, to discuss papers by other investigators and to develop my conclusions based on the history and the geography of the dysmelia And anotia epidemic, and on case histories and documents indicating the time of intake of thalidomide in relation to the stage of pregnancy. I was allowed to give my evidence on 3 consecutive days for a total of about 11 hours. 5 days after my testimony, the cross examination by the defence started and was continued for 12 days, i.e. a total of about 45 hours. The questions presented by the defence covered many sides of the problem, mainly doubtful details of morphology or case history, evading, however, discussion of the decisive facts and arguments.

My comment, expressed to a journalist after the cross examination was:

"They tried to split hairs, but their hairs were not from my fur."

On October 10, 1969, 1 year and 2 months later, the court decided that my testimony could not be used, because the defence lawyers had reasonable grounds for assuming that I was not so unbiased as an expert witness should be. The reasons for assuming my partiality were not inherent to my testimony nor my answers at the cross examination, in which I tried to look at the facts without bias, but derived from previous utterances in letters. I have certainly been somewhat partial in my moral judgement of Chemie Gruenenthal, and my sympathy has not been equally shared between the company and the thalidomide victims, but I took great care not to be influenced thereby in my judgement of facts. Though the decision of the court not to admit my testimony came to me as a surprise, I decided to take it as a compliment to my moral engagement rather than as an offence to my scientific honesty.

The court had its final session on December 18, 1970, 2 years and nearly 7 months after its start. There was neither a sentence nor an acquittal, but the decision that there was no more public interest in continuing the trial, after Chemie Gruenenthal and Urn. Schulte-Hillen and Schreiber, attorneys of the plaintiffs had reached an out-of-court agreement on recompensation of the victims on April 10, 1970. Chemie Gruenenthal had agreed to pay 100 Million German Marks to the children with malformations which could be attributed to thalidomide. The court published a future oriented, balanced evaluation of the whole thalidomide tragedy, confirming that thalidomide was undoubtedly teratogenic and stressing it was more important to change the whole system of development, promotion and sale of drugs, of legal control and of the attitude of doctors and patients, than to find and punish a few individual scapegoats for errors by omission

or commission of a sort which society almost universally had permitted or even encouraged, and which might have occurred in any pharmaceutical company.

On December 17, 1971, the Federal Ministry of Health established the Foundation "Hilfswerk fuer behinderte Kinder" (i.e. institution to help handicapped children), which put the agreement on a legal basis, thereby taking over responsibility for the recompensation scheme.

The committee of trustees, set up to distribute the money given by Chemie Gruenenthal and an additional sum contributed by the Federal Government, asked me to be a member of its medical commission, which was to decide whether a malformation could or could not be attributed to thalidomide and to estimate the amount of damage according to a point scale set up by the commission.

In 1971 and 1972, I gave my opinion on the causation of malformations in about 1,600 cases, and in 1973 on about 800 additional cases. Recompensation, however, started not before December 1972, at first offering a rather small amount averaging about DM 10,000.

In 1973, we were able to fix the final recompensation sum after collecting the necessary medical information by writing some 10 to 20 letters per case. The total sum accorded to an individual case varied from roughly DM 100,000 to DM 180,000.

By September 28, 1973, the Ministry of Health set up detailed instructions for the grant of recompensation in cases of thalidomide damage, including a point scale for fixing the accorded sum in various degrees of damage.

Monthly rent (pensions) varied from DM 100 to DM 450. These amounts were increased by changes of the instructions on August 4, 1976 to be DM 125 to DM 562 per month, and by additional changes of July 1, 1977, February 4 1980 to be DM 141 to DM 635, and August 30, 1991.

Up to December 1991, a total of 538 Million DM have been paid.

The number of thalidomide victims covered by the German recompensation scheme was 2,866.

Countries like Canada, Italy, Japan, Sweden and the United Kingdom were not included in the German scheme, as in these countries other firms than Chemie Gruenenthal had sold thalidomide. The British, Canadian, Japanese and Swedish thalidomide victims got similar recompensation following litigation. The only country in which there appears to be no regulation of recompensation is Italy.

In February 1973, I went to Dublin with Professor Marguardt to examine about 200 Irish children claiming thalidomide damage. While we saw some Irish thalidomide victims with exactly the same types of malformations as we had found in Western Germany to be connected with thalidomide, the majority had a variety of quite different conditions.

The Gruenenthal recompensation scheme included other countries, in which thalidomide had been sold by the German company or produced by licence, such as Austria, Belgium, Brazil, Finland, the Netherlands, Portugal, Syria and Mexico. The malformations attributable to thalidomide in these countries did not differ from those seen in Western Germany, and in cases in which the time of intake was definitely known, it coincided with the sensitive period as

derived from information on German cases. Race, food styles or climate did not appear to play any role.

In 1971, I was asked by Mr. Nishida and his colleagues, attorneys of the plaintiffs in the Japanese thalidomide trial against Dai Nippon Company and the Japanese Ministry of Health, to come to Japan and to serve as an expert witness at the Tokyo District Court. I went to Tokyo on October 21, 1971, where I stayed until November 27.

There were court sessions on two days per week. On the days preceding a session, the attorneys would discuss with me the details of the proceedings of the following day.

The sessions at the Tokyo Court were strikingly different from those at the Alsdorf trial in Germany. Not only was the language much more polite in tone and wording, but the attorneys of the defence appeared to be better informed and more interested in facts and less inclined to bring their opponents out of countenance by insulting insinuations.

From rumours and conversations with several people from both sides I got the impression that the Ministry of Health as well as Dai Nippon were prepared to reach an agreement similar to the German one, and that the plaintiffs thought it preferable to continue the trial in order to get a better position in the coming negotiations.

On November 22, 1972, Mr. Miyatake, President of Dai Nippon, asked me to meet him at his hotel. We had a three hour talk. Mr. Miyatake left no doubt that he was convinced, that thalidomide was the cause of the limb malformation epidemic and that he, as well as the Ministry of Health, were willing to reach an agreement on recompensation.

Three years later, on October 26, 1974, a formal settlement was made at the Tokyo District Court with respect to the 39 families involved in the Tokyo litigation. Similar formal settlements for the litigation's in Kyoto, Osaka, Nagoya, Gifu, Okayama, Hiroshima and Fukuoka shortly followed.

About 300 thalidomide victims were acknowledged by the medical committee set up by the Japanese Ministry of Health. I had been asked to become a member of the committee, and so became involved in evaluating each of these cases during several committee sessions since 1975. The amount paid to the Japanese thalidomide victims were considerably higher than the amounts granted in other countries.

In May 1992, I had the privilege to attend a meeting of the Ishizue foundations and to see 70 thalidomide victims, some of which I had met before in 1965, or in 1971.

https://helix.northwestern.edu/article/thalidomide-tragedy-lessons-drug-safety-and-regulation

THE THALIDOMIDE TRAGEDY: LESSONS FOR DRUG SAFETY AND REGULATION

By: Bara Fintel, Athena T. Samaras, Edson Carias, *Jul 28, 2009*

In a post-war era when sleeplessness was prevalent, thalidomide was marketed to a world hooked on tranquilizers and sleeping pills. At the time, one out of seven Americans took them regularly. The demand for sedatives was even higher in some European markets, and the presumed safety of thalidomide, the only non-barbiturate sedative known at the time, gave the drug massive appeal. Sadly, tragedy followed its release, catalyzing the beginnings of the rigorous drug approval and monitoring systems in place at the United States Food and Drug Administration (FDA) today.

Thalidomide first entered the German market in 1957 as an over-the-counter remedy, based on the maker's safety claims. They advertised their product as "completely safe" for everyone, including mother and child, "even during pregnancy," as its developers "could not find a dose high enough to kill a rat." By 1960, thalidomide was marketed in 46 countries, with sales nearly matching those of aspirin.

Around this time, Australian obstetrician Dr. William McBride discovered that the drug also alleviated morning sickness. He started recommending this off-label use of the drug to his pregnant patients, setting a worldwide trend. Prescribing drugs for off-label purposes, or purposes other than those for which the drug was approved, is still a common practice in many countries today, including the U.S. In many cases, these off-label prescriptions are very effective, such as prescribing depression medication to treat chronic pain.

However, this practice can also lead to a more prevalent occurrence of unanticipated, and often serious, adverse drug reactions. In 1961, McBride began to associate this so-called harmless compound with severe birth defects in the babies he delivered. The drug interfered with the babies' normal development, causing many of them to be born with phocomelia, resulting in shortened, absent, or flipper-like limbs. A German newspaper soon reported 161 babies were adversely affected by thalidomide, leading the makers of the drug—who had ignored reports of the birth defects associated with the it—to finally stop distribution within Germany. Other countries followed suit and, by March of 1962, the drug was banned in most countries where it was previously sold.

In July of 1962, president John F. Kennedy and the American press began praising their heroine, FDA inspector Frances Kelsey, who prevented the drug's approval within the United States despite pressure from the pharmaceutical company and FDA supervisors. Kelsey felt the application for thalidomide contained incomplete and insufficient data on its safety and effectiveness. Among her concerns was the lack of data indicating whether the drug could cross the placenta, which provides nourishment to a developing fetus.

She was also concerned that there were not yet any results available from U.S. clinical trials of the drug. Even if these data where available, however, they may not have been entirely reliable.

At the time, clinical trials did not require FDA approval, nor were they subject to oversight. The "clinical trials" of thalidomide involved distributing more than two and a half million tablets of thalidomide to approximately 20,000 patients across the nation—approximately 3,760 women of childbearing age, at least 207 of whom were pregnant. More than one thousand physicians participated in these trials, but few tracked their patients after dispensing the drug.

The tragedy surrounding thalidomide and Kelsey's wise refusal to approve the drug helped motivate profound changes in the FDA. By passing the Kefauver-Harris Drug Amendments Act in 1962, legislators tightened restrictions surrounding the surveillance and approval process for drugs to be sold in the U.S., requiring that manufacturers prove they are both safe and effective before they are marketed. Now, drug approval can take between eight and twelve years, involving animal testing and tightly regulated human clinical trials.

Despite its harmful side effects, thalidomide is FDA-approved for two uses today—the treatment of inflammation associated with Hansen's disease (leprosy) and as a chemotherapeutic agent for patients with multiple myeloma, purposes for which it was originally prescribed off-label. Because of its known adverse effects on fetal development, the dispensing of thalidomide is regulated by the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program. The S.T.E.P.S. program, designed by Celgene pharmaceuticals and carried out in pharmacies where thalidomide prescriptions are filled, educates all patients who receive thalidomide about potential risks associated with the drug.

Thalidomide has also been associated with a higher occurrence blood clots and nerve and blood disorders. Northwestern University's pharmacovigiliance team, Research on Adverse Drug Events And Reports (RADAR), has launched a joint project with the Walgreens pharmacy at Northwestern Memorial Hospital so that these side effects may be understood and monitored, like those affecting fetal development. RADAR, led by Dr. Charles Bennett of the Feinberg School of Medicine, combines the expertise of clinicians, academics, pharmacists, and statisticians to monitor and disseminate information about adverse drug reactions to cancer drugs.

Their project tracks the number of patients who get a blood clot after receiving thalidomide, whether or not the patient received an anticoagulant drug, which are used to help prevent clotting, and if so, which drug was used. Tracking this information will help researchers better identify the incidence and prevention of thalidomide-associated blood clots, allowing the drug to continue to serve as an effective therapy for many patients.

To prevent the serious side effects associated with thalidomide, the S.T.E.P.S. program tightly regulates its distribution. The examples listed below are just a sampling of the measures in place:

-Product labeling that indicates the risks of thalidomide
- Required registration of all prescribers, patients, and pharmacists who prescribe, receive, or dispense thalidomide
- A patient acknowledgement / informed consent form
- A required telephonic survey that patients and prescribers must complete.
- Required pregnancy testing in females of childbearing potential
-Compliance with measures to prevent pregnancy and thereby prevent fetal exposure to thalidomide
-Educational materials
-Patient counseling
-Limiting prescriptions to a 28-day supply
-Prohibition of telephone prescriptions and automatic refills