The Same and Not the Same

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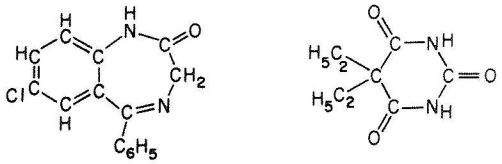
27. Thalidomide

Chemie Grünenthal was one of many small pharmaceutical firms in postwar Germany. It first made antibiotics for other companies, but in the 1950s the firm ventured into its own modified penicillins. The German drug market was quite open then; neither the efficacy nor safety of a drug had to be proven in great detail. Almost anything was available over the counter, and the success of a product depended as much on advertising and marketing as on its value.[1]

It was in the 1950s that Valium and Librium were introduced, tranquilizers which were an instant success. Illustration 27.1 shows the structure of diazepam (Valium) as well as barbital (Veronal), a com-



diazepam (Valium)

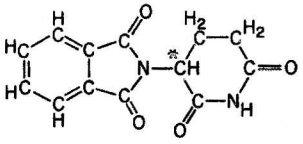
barbital (Veronal)

27.1 The structure of diazepam (Valium; *left*) and barbital (Veronal; right)

Much of the information in this chapter is drawn from Henning Sjöström and Robert Nilsson, *Thalidomide and the Power of the Drug Companies* (Harmondsworth: Penguin, 1972).

mon barbiturate sedative. It was natural for pharmaceutical companies to explore compounds that were chemically similar, even in the vaguest way, to these molecules. There was a lot of money to be made in the sedative and tranquilizer market.

Given its size, Chemie Grünenthal had only a small scientific department, headed by a physician, Dr. Heinrich Mückter. In 1954, Wilhelm Kunz, a chemist on his staff, by training actually a pharmacist, synthesized (N-phthalidomido)-glutarimide ("thalidomide"), the molecule whose structure is shown in illustration 27.2. Note the superficial resemblance to the sedatives shown above. Note also the presence in thalidomide of a carbon with four different groups around it (marked by an asterisk in illustration 27.2), pointing to the existence of enantiomers, nonsuperimposable mirror images. The molecule as used medically was a mixture of the two enantiomers.



thalidomide

27.2 The chemical structure of thalidomide.

Driven by the resemblance I've pointed to, the Chemie Grünenthal researchers convinced themselves that the molecule had good sedative properties. The reason I say it in this way is that subsequent investigations have failed to confirm the sedative qualities claimed. The toxicity of thalidomide was low, and this encouraged the manufacturers to put the drug on the market. It was first introduced as part of a drug combination directed toward respiratory infection in 1956 and shortly thereafter sold as a sedative directly and in dozens of combinations in Germany.

The company needed published articles testifying to the utility of the drug. So it sought them out. In the Grünenthal files there is a report from their Spanish representative that a certain doctor "had declared he was prepared to write a short report on Noctosediv [the Spanish trade name for thalidomide] whereby he would leave it to us to revise the final draft." In the United States, in 1959, Ray O. Nulsen, a Cincinnati physician, was convinced by Dr. Raymond Pogge, the medical director of Richardson-Merrell, the American company that was try-

ing to market thalidomide under license from Grünenthal, to "test" the drug. Here is part of Nulsen's deposition in a subsequent trial (Spangenberg is an attorney taking the deposition before the Eastern District Court of Pennsylvania):

> "I note, doctor," Spangenberg said "that he (Dr. Pogge) asked you to start testing promptly and to send in reports. Do you have copies of the reports you sent in?"
>
> "No, it was all verbal," Dr. Nulsen replied.
>
> Dr. Nulsen later said he had passed on the testing information to Dr. Pogge "by telephone, or it may have been that we had lunch together, or it may have been when we played golf." . . .
>
> This information was eventually collected in an article published under Dr. Nulsen's name in the June 1961 issue of the *American Journal of Obstetrics and Gynecology,* entitled "Trial of Thalidomide in Insomnia Associated with the Third Trimester." This rather detailed publication put forward the conclusion: "Thalidomide is a safe and effective sleep-inducing agent which seems to fulfil the requirements outlined in this paper for a satisfactory drug to be used late in pregnancy."
>
> Spangenberg: "Who wrote the article, Dr. Nulsen?"
>
> Dr. Nulsen replied, "Dr. Pogge. I supplied him with all the information."
>
> At another point the attorney asked, . . . "your article cites about half a dozen German magazines and German texts. [Dr. Nulsen did not read German] Did you ever read these articles?"
>
> Nulsen: "No. That was supplied to me."
>
> Spangenberg: "You also cite Mandarino, another doctor, and footnote the citation, and the footnote reads, 'To be published.' Did you ever see his article?"
>
> Nulsen: "I don't remember having seen it."[2]

It turns out that in fact thalidomide is safe in the third trimester of pregnancy. But the quality of the research cited here was at the time unfortunately typical of the work of Chemie Grünenthal and its associated companies.

Henning Sjöström and Robert Nilsson, who have participated actively in the legal processes around thalidomide, cite another case in their devastating book:

> During the early part of 1961 the Stolberg company [Chemie Grünenthal] was told of a Dr. Davin Chou in Singapore who had successfully used thalidomide for the treatment of pregnant women. No details were given about the stage of pregnancy treated, the dosage used or the frequency of therapy. Finally, and most significantly, the brief report was

> concerned only with the effect on the pregnant women themselves, and no mention was made of any possible effect on the fetuses. This lack of any specific detail did not deter Dr. Werner [a director of Grünenthal's medical-scientific department] from distributing a circular letter to "co-workers throughout the world" saying, "In a private clinic in Singapore Softenon [thalidomide] was given to pregnant women who tolerated the drug well."[3]

In 1958, Dr. Augustin P. Blasiu in Munich published an article in *Medizinische Klinik* in which he said, "Side effects were not observed with either mothers or babies." He had administered thalidomide to 370 patients, but only to nursing mothers. Chemie Grünenthal sent a letter to 40,245 physicians citing Blasiu's work, describing thalidomide as a drug "which does not damage either mother or child."[4]

In 1959 reports began to come in about severe neurological damage, neuritis, caused by thalidomide. These were steadfastly denied, obfuscated, and concealed by the Grünenthal people; and numerous attempts were made to stifle public reporting of these symptoms. Worse was to come.

In 1960 physicians in Germany and Australia noticed a striking incidence of a peculiar malformation in newborns. It was phocomelia, a deformity in which the hands are attached to the shoulders, and feet to hips, like the flippers of a seal (hence the name of the syndrome: Greek *phoke* = seal, *melos* = limb). The anomaly was sufficiently rare prior to that time (estimated incidence: one case in four million births) that most physicians had never seen a case.

These were not the only symptoms. To quote a Canadian study of the mothering of thalidomide children:

> Limb-deficiency, though the most common and most striking anomaly, constituted only one element of the syndrome among a host of other deformities. The major external defects were coloboma (a defect in one or both eyes), microtia (smallness of the external ear) associated with partial facial palsy, depressed bridge of nose, and hemangioma (tumor) on forehead, cheek, or nose. The internal defects were found in the cardiovascular system, urogenital system, and intestinal tract; there were also abnormal lobulations of liver and lungs, dislocated hips, syndactyly (fusing of fingers or toes), horseshoe kidney, bicornuate uterus, atresia (closure of a normally open channel in the body), and absence of the gall bladder.[5]

27.3 Goya brush and wash drawing, *Mother Showing Her Deformed Child to Two Women.* In the collection of the Louvre, reproduced by permission.

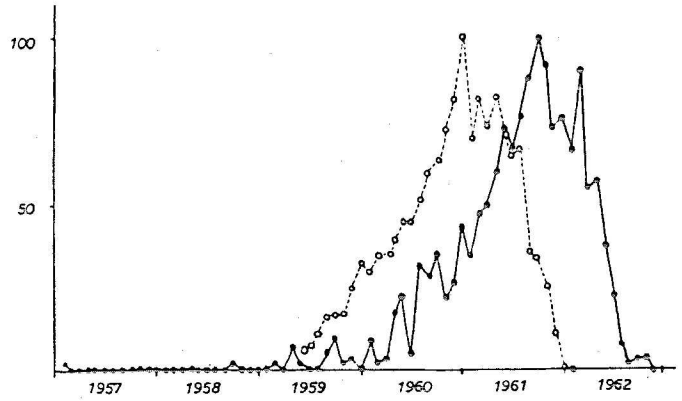
Goya, that prescient explorer of the dark side of our world, drew a "natural" case of phocomelia. This is shown in illustration 27.3.[6]

Approximately eight thousand children were born alive with phocomelia or related abnormalities. Most of these were in Germany and England, but there were cases reported in some twenty countries. Only after the evidence mounted so that it could not be excused or argued away and after exposure in the press did Chemie Grünenthal withdraw the drug from the German market, in November 1961. The various

drug companies around the world who licensed the drug followed suit, unconscionably slowly.[7]

Did thalidomide cause the terrible abnormalities observed? Animal testing done *after* the disaster clearly showed the teratogenic (malformation causing) nature of the drug. Thus monkey tests at Pfizer showed *every* embryo deformed when the mother was given thalidomide in a certain early period of pregnancy.[8]

Do you want another kind of proof? Examine illustration 27.4,[9] which shows the incidence of thalidomide-type birth malformations in Germany and thalidomide sales, both "normalized" to the same value at their highest point.



27.4 Incidence of thalidomide-type malformations (solid line, normalized to 100 in October 1961) and thalidomide sales (dashed, normalized to 100 in January 1961). Reproduced by permission of Churchill-Livingston Ltd.

Now we must face some of the obvious issues raised by this terrible story.

1.

Is thalidomide a *chemical* disaster? There seems to be only one chemist in the story, Wilhelm Kunz. Significantly, he was not one of the defendants in the ultimately futile legal process (1967–1970) instituted against Grünenthal in Germany, a trial vitiated by a compensation settlement between the company and the parents of the "thalidomide

children." Of the seven principals in the case, five were physicians. The company's deceit of the public was mainly managed by doctors—*and* by the owners and management of the firms involved. So why blame this on chemistry?

I think there are two reasons for chemistry to share in the guilt. Thalidomide is a chemical. Chemists like to lambaste the public for its ignorance of the distinction between the natural and the unnatural. Indeed they are right to do so. But once you have taught people the chemical nature of all matter, and that the natural may sometimes hurt you, you must not try to hide that the synthetic also may, sometimes, hurt. This chemical did harm.

The worldwide public now has a variety of "chemical disasters" to choose from. There was the catastrophe of Bhopal in India (and there will be another one). There are tank cars of benzene or chlorine that are derailed. There is DDT; there are chlorofluorocarbons. There was mercury poisoning in Japan as there is currently in Brazil. I could have discussed any of these. In each case one could argue for an exculpation—this or that is not chemistry. Or even for a positive role for chemistry; who but chemists F. Sherwood Rowland and Mario J. Molina found the connection of chlorofluorocarbons to ozone depletion?

In each case economics and its dark side, greed, are dominant. But if chemists take credit for the positive trade balance contributions and the ulcer drug Tagamet, we also have to be willing to accept the blame. At least part of it. No chemist at Grünenthal (or another company) voiced any public doubts about the firm's behavior as reports of harmful effects just flooded in. No one blew a whistle. Only other physicians, and a free (and, yes, sensationalist) press, did.

There is another curious chemical angle to the thalidomide story. The molecule has one carbon in it with four different substituents around it. So thalidomide is chiral; this means, as we saw, that it exists in nonidentical handed forms. The reaction that produced it initially gave equal amounts of the left- and right-handed forms. And so it was used. There is some indication (contended) that the two enantiomers differ vastly in teratogenicity. The matter is somewhat complicated by the fact that the "harmless" enantiomer converts into the "harmful" one under physiological conditions.[10] The world is never simple . . .

Clear cases of differing biological activity of mirror-image forms of one and the same molecule abound. D-penicillamine is widely used in the treatment of Wilson's disease, cystinuria, and rheumatoid arthritis. Its optical isomer gives severe adverse effects.[11] The enantiomer of a

tuberculosis drug, ethambutol, can cause blindness. Disastrous side effects associated with the painkiller benoxaprofen might have been avoided if the drug had been sold in its one-handed form. Such cases have led to regulatory pressure encouraging testing of pharmaceuticals as pure enantiomers. Some chemists and drug companies have resisted this, but others have realized there is creativity in designing handed syntheses. And profit.[12]

The twenty-five top-selling prescription drugs in the United States sold for $34.4 billion in 1993. Of these sales, 25 percent were of molecules that are not chiral, 11 percent were marketed as a mixture of the two mirror images, and 64 percent as one enantiomer. The handed category has been increasing at the expense of the mixture of enantiomers; in time all chiral drugs will be sold in a single, handed formulation.[13]

2.

Surely this (the behavior of Grünenthal, Richardson-Merrell Distillers, Astra, Dainippon, and others) is just bad science, isn't it? Just look at those quotes from the Spanish, American, and Chinese doctors! Were the science (pharmacology, biology, medicine, chemistry) done well, or at least just plain adequately, this would not have happened.

Indeed animal testing for teratogenicity of new drugs was routine in the major pharmaceutical companies. Hoffmann-LaRoche's Roche Laboratories published a major reproductive-system study of its Librium in 1959. Wallace Laboratories did so for Miltown in 1954. Both instances antedate the thalidomide story. Dr. Frances Kelsey, the FDA physician who courageously resisted enormous Richardson-Merrell pressure to license thalidomide in the United States, had good reasons for her reluctance. As a student in 1943 she demonstrated (with F. K. Oldham) that the rabbit fetus could not break down quinine, while the liver of the adult rabbit does so effectively.

The answer is twofold, I think. First, yes, this is abysmal science. And whereas science as a system for gaining reliable knowledge works in spite of instances of poor-quality experimentation—it will easily survive sloppiness, hype, and even fraud—the kind of science that touches on human lives cannot afford to be bad. The thalidomide disaster should not have been allowed to happen. Yet not a single drug company (all that competition in the sedative market!), not a single individual screamed, either before, or during, while thousands of adults suffered from neuritis and children were born into a less than fully human life.

The system failed. Science and medicine (chemistry in part) failed. The remedy had to come from legislation on drug testing that slowly was introduced around the world in the 1960s.

The second answer, I think, is, yes, this is bad science. But it isn't just bad science. It is an insidious failure of the system, because it intersects with the banality of evil, in Hannah Arendt's famous phrase. None of these people—the unethical doctors who supplied the results the company wanted, the salesmen in the field, the manipulators and distorters of data such as Dr. Mückter, the lawyers, men who threatened legal action against the physicians who first reported side effects, the medical journal editors who stalled on publication because a company objected—none of these were just plain evil. I'm sure they were good but flawed men (maybe even a woman here and there) who each in their own little way heard and saw something, but then in the gray area between doubting (as they should have) or following company policy, in that moral neither here nor there, neither black nor white land, they chose just a little here, just a little white. They then passed along a selected, slightly distorted message to human beings of similar moral weakness, who massaged the data just a little bit more, ignored what they didn't want to see, refused to read that memo with the bad news in the file, attributed that reaction to hysteria.

3.

So the outcome was bad. Then legislation cured the problem—but now haven't we gone overboard? The creativity of the drug designer is stifled; it costs $100 million to bring a drug to the market just because of all those mandated safety and efficacy tests. The net results, so this argument goes, is that we have kept more drugs from the market and thereby indirectly lost the lives of many people.

When I hear this argument, I am tempted to do what I do not want to do, and show the picture of a thalidomide child. It is not a matter of how many lives might have been lost because of the more stringent rules preventing new drugs, but of how many lives have been saved because the regulations prevented more thalidomide-like disasters.

If there be a calculus of risks and benefits, then the weighting that is applied to a single drug-induced phocomelia birth is (to me) so great that it outweighs any life or hundreds of lives saved. The anguish of the eight thousand thalidomide children and their parents is unimaginable. Nothing in the world can justify this. It must not happen again!

The theme of the same and not the same arises so clearly in the

thalidomide story. The makers and sellers of the drug chose to see its resemblance to other sedatives and tranquilizers. They chose not to see the possibly different effectiveness and toxicity of the mirror-image forms of the molecule.

Primo Levi, in his wonderful autobiographical history, *The Periodic Table,* tells the story of an explosion he had while doing some research at the University of Turin. He needed sodium to dry an organic solvent, but he used instead potassium, another alkali metal, right under sodium in the periodic table. He writes of what the experience meant to him:

> I thought of another moral . . . and I believe that every militant chemist can confirm it: that one must distrust the almost-the-same (sodium is almost the same as potassium, but with sodium nothing would have happened), the practically identical, the approximate, the or-even, all surrogates, and all patchwork. The differences can be small, but they can lead to radically different consequences, like a railroad's switch points; the chemist's trade consists in good part in being aware of these differences, knowing them close up, and foreseeing their effects. And not only the chemist's trade.[14]