# Thalidomide: A Villain Reformed?

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In 1954 chemists from Chemie Grünthal, a small, West German pharmaceutical company, heated phthaloylisoglutamine. They were trying to find a simple, inexpensive technique for making antibiotics, but the product, which they named thalidomide (from the Greek *thalia* meaning joy or blooming), was not an antibiotic. Animal tests showed no sedative or anti-tumour effects, but also no toxic effects even at high doses, and so clinical trials were attempted. These showed that thalidomide put patients into a deep, all-night natural sleep.

Thalidomide was released in West Germany on 1st October 1957 as a safe and effective sleeping pill, even for pregnant and nursing mothers, under the name Contergan. Distillers Company (Biochemicals) obtained market rights for the UK and began distributing thalidomide under the name Distaval in April 1958. It soon became the drug of choice to help pregnant women combat morning sickness. However, doctors began to notice that some patients developed "peripheral neuritis", a condition that causes tingling and loss of sensation in the limbs. This was irreversible in some patients.

By 1960 an extremely rare type of birth defect, phocomelia, was being detected where babies were born with hands and feet directly attached to the body. Slowly these defects were linked to thalidomide, and on 26th December 1961 the *Lancet* and the *British Medical Journal* published a letter from Distillers Company (Biochemicals) of Liverpool, stating that thalidomide had been withdrawn from the UK market. Four months after thalidomide was withdrawn from the market George Somers, of Distillers, reported that high doses of thalidomide in rabbits could cause limb defects in the offspring. The absence of similar results in other animals is still not understood.

It is estimated that between ten and twenty thousand thalidomide babies were born, of which around five thousand survive today. It is not known how many more babies miscarried or were stillborn as a result of the drug.

The history of thalidomide could have stopped there but for chance; in 1964 Jacob Sheskin at the Jerusalem Hospital for Hanesn's Disease found a bottle of thalidomide and gave a patient two tablets to help him sleep. The patient was critically ill with Erythema Nodosum Laprosum (ENL), an advanced inflammatory complication of leprosy, and was in such severe pain that he hadn't slept in weeks.

The man slept for 20 hours and upon waking was able to get out of bed. After two more tablets his pain disappeared. Six other Hansen's patients were treated with similar results. Further study showed that 99 per cent of patients improved and 35 years later thalidomide still remains the drug of choice for ENL.

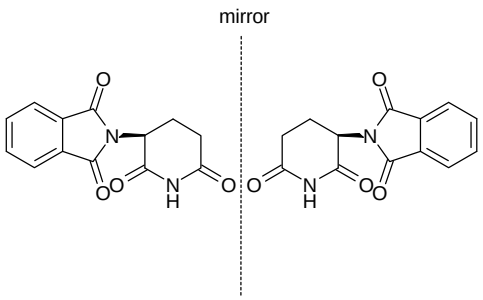
In 1991 Gilla Kaplan demonstrated that thalidomide decreases TNF-α levels *in vitro* and in ENL patients. Kaplan also proposed that thalidomide might combat wasting from tuburculosis, a major problem for AIDS patients. In 2000 Kaplan demonstrated that, although thalidomide does not decrease TNF-α

levels in AIDS patients with tuberculosis, it does enhance their immune response. Kaplan's group reported that thalidomide also inhibits replication of the HIV virus *in vitro*, but stimulates replication *in vivo*.

In 1992 the opthalmologist Robert D'Amato was looking for an anti-angiogenic, anticancer drug. He theorised that an anti-angiogenic drug would interfere with menstrual cycles and as angiogenesis also took place in the early stages of foetal growth it may cause birth defects. He came up with a list of six potential anti-angiogenic drugs, one of which was thalidomide. In tests on chick embryos D'Amato established that while thalidomide itself did not inhibit angiogenesis, its metabolites did. The group also used thalidomide to stop angiogenesis in the corneas of rabbits, which they had previously stimulated with the compound fibroblast growth factor.

Based on these studies Bart Barlogie carried out studies of the effect of thalidomide on patients with advanced multiple myeloma, an incurable and usually fatal cancer of the bone marrow. Enhanced angiogenesis is one of the characteristic symptoms of the disease. The study led to interesting results: about a third of the patients showed a significant reduction in cancer progression, whilst two of the patients achieved complete remission.

The method of action of thalidomide is still being investigated. Thalidomide occurs in two chiral forms (known as enantiomers): two compounds which are mirror images of each other, but cannot be superimposed, analogous to the situation seen with your left and right hands. It was synthesised as a racemic mixture, that is an equal amount of the *R* and *S* enantiomers. It has been shown that the *R* enantiomer is responsible for the drug's anti-inflammatory activity, whilst the *S* enantiomer is responsible for its teratogenic activity. So can the side-effects of thalidomide be prevented by giving only the *R* enantiomer? The answer, unfortunately, is no, as the liver contains an enzyme that converts the *R* into the *S* enantiomer.




**Thalidomide:** the two enantiomers are mirror images but not superimposable on each other

Celegne, a US pharmaceutical company, has developed and tested numerous analogues of thalidomide. They, in collaboration with Kaplan, have demonstrated that thalidomide, and several of its analogues, not only inhibit TNF-α, but also stimulate T cell responses. Some of the thalidomide analogues are 50,000 times more potent than thalidomide itself. In 2000 the researchers demonstrated that one class of thalidomide analogues, the immunomodulatory drugs (ImiDs) act directly on multiple myeloma cells by inducing cell death and/or by arresting cell growth. These actions appear to overcome the classical drug resistance that hampers treatment of this incurable disease.

So what is the future for thalidomide? The drug itself is still being used and shows promise in treating several diseases, although the potential consequences of its use are still very much present; in Brasil, where the drug is sold for leprosy, another thalidomide generation has appeared. Analogues of thalidomide are being developed, and hopefully, one day, an analogue will be found which possesses thalidomide's benefits without a trace of its devastating side effects.