It's Back

Thalidomide is the most famous bad drug in history. So why is it coming back?

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Towards the end of last month, 115 people with no arms or legs gathered in a small village in southern Sweden to talk about their common interests. All in their mid-30s, most of them seemed to like the same sort of music and sport. They came from all over the world, but they had a similar taste in clothes, food and beer.

They shared one more thing: their mothers had all taken thalidomide between 1957 and 1962, primarily as a sedative, a sleeping pill, something that could calm nerves and help with morning sickness. Great claims were made for the drug, not least that I was completely non-toxic. Unlike other barbiturates, thalidomide was considered so safe that even pregnant women could take it. So they did, many thousands of them, and a small fraction of their 10,000 offspring are now in a large hotel in Sweden discussing all the things that concerned them most: compensation, ageing, pain-relief, mobility.

This was only the second time such an international gathering had been organised – the first was four years ago – and people had come from Japan, Scotland, Germany, Canada and the Netherlands to attend. As they talked in the bar, there was a new topic of conversation, one that had rarely occupied them before, and one which they believed they would never ever have to confront. Thalidomide was making a comeback, and not in a shy way.

They had learned that the drug now had up to 50 trade names, and was being manufactured in the United States, Canada, Brazil and Wales. In Germany it was being made by the same company that had patented it almost 40 years ago. This time it was not being sold as a sedative, but for a large number of uses for which it was never intended. In Brazil and Israel it helped those with leprosy. In the United States it prevented a major cause of blindness. In the UK it was being used for two severe symptoms of HIV and Aids. Throughout Europe it was found successful in graft-versus-host disease, a common complication of bone marrow transplants. And, throughout the world, it was being tried for cancer, tuberculosis and rheumatoid arthritis. Some medical researchers were talking of it as a panacea, almost a miracle.

The ingredients of the drug remained the same as they had always been. Perhaps now it was a little purer than it used to be, and came in soluble capsules rather than tablets. It was called thins like Sauramide and Synovir. With so many varied diseases to treat, thalidomide could now be used by so many more people than had used it in the Fifties and Sixties. The potential

side-effects – so many babies born dead, or with missing or deformed limbs, or with damaged internal organs – remained the same.

Alongside aspirin, thalidomide can lay claim to being the most famous man-made drug of all time, but only because of the suffering it caused. If a woman took it during the first trimester of her pregnancy, certain things would happen to the growth of her foetus. Between the 20th and 25th days of development, there would be defects of the ears and eyes; between 26 and 30 days, there would be defects on the arms; between 31 and 35 days, there would be defects on the legs. If she took thalidomide all through this period, her baby, if born at all, might emerge merely as a trunk, with no limbs and severe organ damage. At the time of thalidomide's first appearance, none of this was known. But it is now known with certainty, which makes the current proliferation of new uses all the more extraordinary.

Towards the end of 1993, Robert D'Amato, an ophthalmologist working at Harvard Medical School in Boston, made an important discovery. D'Amato, 33, specialised in the study of blood vessels, and was particularly concerned with how their growth affected eye diseases like diabetic retinopathy (the most frequent cause of blindness in people aged between 20 and 60) and senile macular degeneration (the leading cause of blindness in those over 65). Both conditions are brought on by blood vessels multiplying t abnormally high rates.

He set out to find a drug that could stop blood vessels from growing. He believed that, if this drug existed, it would do two things: stop women's menstrual cycle, a process during which blood vessels grow and bleed before they shed; and it would interfere with the development of the foetus, as the foetus consists of rapidly growing blood vessels in developing limbs and organs.

When D'Amato tapped his computer in search of suitable compounds, he found thousands of possible drugs that would do one or other, but only a handful that would do both. One of these was thalidomide. "At the time, I thought it was a really shocking thing," he says. "But it did all fit. Maybe this is why thalidomide caused birth defects in the first place. Then I thought, maybe it could be used in a good setting."

Why did this realisation take so long? Mostly because people have only been able to grow blood vessels very recently. "I may not be the first person to have had the idea," D'Amato says. "I'm just the first person to have had the idea at a time when it could be tested. People didn't really think of blood vessels as a growing organ back then. Even if someone had this idea in 1957, they could never have proved it. That, of course, is the tragedy."

It was in 1957 that thalidomide was first mass-produced in Germany, by Chemie Grünenthal, a small and relatively new company set up during the post-war boom in antibiotics. In thalidomide, it believed it had a product that would come to dominate a large and lucrative market; then as now, the pharmaceuticals industry was governed by mammon, and other barbiturates

and other artificial relaxants were a booming business. Companies would rush a product out of the door as soon as the rules would allow.

Thalidomide was licensed with haste throughout the world. In Britain, where it was sold as Distaval and Distaval Forte, it was marketed by Distillers (Biochemicals) Ltd, whose parent company was better knows for manufacturing whisky and other spirits. Only in the United States did more stringent controls ensure that thalidomide did not gain a licence until further research was conducted. One American drugs administrator remembered what everyone else had forgotten: that the only drug with no level of toxicity or potential side effects would be one that was completely useless.

The tragedy was first uncovered in May 1961, but it took until the end of that year for the drug to be withdrawn in Germany and Britain. In other countries, the drug continued to be sold well into the following year. The scandal made front-page news for months, but the full details remained shrouded for a decade, obscured by the secrecy and judicial injunctions employed by drug companies and governments as parents and lawyers established liability and sued for compensation.

The thalidomide experience transformed the pharmaceutical industry: by the time Distillers withdrew from the drugs business in 1962, new medicine control guidelines were already coming into place in Britain and throughout the West. And it transformed the public perception of modern science: the medical profession was omnipotent no longer.

The 10,000 babies affected by thalidomide is only a rough estimate, for it is impossible to calculate the amount of miscarriages or stillbirths attributable to the drug. Thalidomide was prescribed in 46 countries. About 2,000 of those born alive are alive today. About half live in Germany, and there are 458 in the UK.

More than 30 years on, thalidomide still occasionally hits the headlines. There are campaigns for further compensation, and claims that the drug may go on to affect the children of the disabled. But the full tragedy is fading from memory, and perhaps we should not be surprised to learn that among ambitious, young medical researchers the episode is now little more than a page in a textbook, a calamity that could never be repeated.

Robert D'Amato is fully aware of thalidomide's history, and so are his patients. "Everyone knows of the possible terrible side effects," he says. "We just have to use these drugs responsibly. What we really have to worry about is drugs that cause birth defects that we don't know about. If you know the dangers, you can be hyper-vigilant."

In April 1995, several months after preliminary tests on rabbits confirmed his findings, he set up the first trail of thalidomide on 60 people with macular degeneration. The trail will last two years, after which he will discover whether the drug slows the loss of vision. Positive results will lead to further trials, with hundreds of patients, to test the idea dosage and other safety factors. His patients receive two months' supply between each visit. Although

the women are all post-menopausal, they are told to keep their new drug in a locked case.

D'Amato hopes thalidomide may again be commercially available in four or five years, and that it may save the sight of 1.5million Americans and many more worldwide. Apart from laser treatment, which is only partially effective and very expensive, he says that, at present, there is nothing else that might do the trick.

As with nuclear weapons, once a drug is invented, the process cannot be reversed. The rehabilitation of thalidomide has been going on since 1965, when an Israeli doctor gave it as a sedative to leprosy patients. By chance, their skin lesions cleared up simultaneously. Ever since, it is believed that hundreds of thousands have taken the drug in South America and India, mostly for the symptom *trythema nodosum leprosum* (a side effect of the leprosy drugs), but also for stomach disorders, skin grafts and severe oral and genital ulceration. Supplies came mainly from Brazil and, to the distress of many Germany thalidomide victims, from resumed production at Chemie Grünenthal.

And so, through misadventure and persistence, a bad drug was slowly shown to do good. There is not more extreme example of a medicine that may turn out to have so many other valuable uses that that for which it was first designed.

Thalidomide's anti-inflammatory activity was studied in international medical literature, but until 1989, the central question remained unanswered: how did it work? A team at Rockerfeller University in New York made the breakthrough when it found that thalidomide reduced the body's production of TNF-alpha, a fluid chemical that emerges from human cells to send messages to other parts of the body. Balanced levels of TNF-alpha are believed to be crucial to the correct functioning of the immune system. Overproduction causes weight loss and fevers, and excessive amounts are often found in people with HIV. In the United States, test-tube experiments have shown that thalidomide inhibits not only TNF-alpha but also reproduction of the virus, and there are already signs closer to home that the drug may be used against specific and devastating symptoms of Aids in unique ways.

Dr Mike Youle, research director of the Kobler Centre, the HIV unit of Chelsea and Westminster Hospital, says he has given thalidomide to about 150 patients for severe mouth ulcers, and has seen dramatic results. Although 95 per cent of his patients are gay men, one of the first to receive thalidomide in the late Eighties was a woman, and he received much criticism for administering it.

"I pointed out that that she was in a hospital bed, on a morphine drip, with a tube down her throat to feed her because she had massive ulcers in her gullet, and that she had HIV and various other infections, and it was relatively unlikely that she was going to get pregnant. We had actually discussed the issue before we gave it to her. But here was this overall idea that, immediately

you give the drug to someone, they're then going to immediately rush off and get pregnant, just to annoy everybody."

Youle is 35. Most of his patients are his age or younger. In his cramped office above the Fulham Road, he has supplies of the patient consent forms that the Medicines Control Agency stipulates must be given to all thalidomide users. As he says, "If you were a gay man of 23, why would you know anything about it?"

The form contains a brief history of the drug and a list of common side effects, including skin rash, sore throat and peripheral neuropathy – a loss of feeling in the hands and feet. There are also some instructions in bold type: "You should never give these capsules to anyone else or leave them in a place where others may have access to them; if you are pregnant, or likely to become pregnant, do not use these capsules. If you discover you are pregnant while taking these capsules, tell you doctor immediately."

Youle says that the biggest issue is always potential accidental use by someone else. "But this dilemma is a common occurrence for us: we are giving experimental therapies the whole time." He reads out a list of other drugs women are not allowed to take unless they are also using barrier contraception. "You could argue that, if you wanted to be 100 per cent save about every drug, you'd have to take paracetamol off the market. Something that occurs as a one-off event is always more exciting than something that occurs over a long period of time. It's like Haley's Comet: it's not the most exciting thing in the world, but it only occurs once every 76 years, so everybody gets very excited about it. Actually, something that happens every day, like the aurora borealis, which you have to make the effort to go and see, is much more interesting. That's a bit how I feel about the thalidomide problems in pregnant women."

Youle's attitude to prescribing thalidomide is changing. Now there are other ways of treating mouth ulcers, and often they are as effective. Accordingly, these days he thinks he would prefer to administer oral steroids. "However," he says, "if I had a woman who was shitting themselves to death, and I could give thalidomide, then I would." He is referring to *microsporidosis*, another symptom of HIV, and a life-threatening one. With *microsporidosis*, there are huge levels of TNF-alpha in the gut. It seems that this torrential diarrhoea and abdominal bloating in people with damaged immune systems can also be cleared up with a few capsules of an old drug.

Youle and his colleagues have treated about 20 patients with thalidomide for *microsporidosis*, and they report marked benefits in a condition that is relatively hard to treat in other ways. In one extreme example, a man weighing 60 kilos was visiting the toilet up to ten times a day, and this had been the case for about a year. Three days after taking thalidomide, his diarrhoea stopped and he put on ten kilos.

This use of thalidomide will soon be the focus of a controlled trial conducted with the Celgene Corporation of New Jersey, the company with the largest thalidomide research programme in the United States. The Kobler Centre will

also combine with Celgene on a trial to determine the optimum dosage and levels of absorption of the drug. Mike Youle suggests there is still so much we don't know about thalidomide. "The research is inadequate because it was withdrawn fairly quickly and (the tragedy) did not affect America," he says. "That's the reason there is so much HIV research done – because it's hit America. If HIV only affected the UK, then we'd have hardly any research at all. There's money to be made – the realities of life."

At the end of August, Celgene was granted permission by the US food and Drug Administration to conduct a large, open-access clinical trial into Aids-related wasting. One effect of this trial, which is open to women, will be a reduction in the amount of impure, imported thalidomide which is bought and sold in illicit buyer-clubs, a common resource of unlicensed Aids treatments.

The Kobler Centre receives its supplies from David Erskine, the HIV pharmacist with an office in another part of the hospital Erskine used to get it from Brazil. "It came in dodgy, little white powdery tablets," he remembers, and he wasn't sure just how much thalidomide there actually was in each tablet.

"We had meetings about the ethical considerations, and it was decided that the benefits outweighed the risks, provided there were very strict controls about how many tablets were given out. There were strenuous efforts to ensure that unused tablets were brought back and destroyed.

Are these safeguards enough?

"I'm not sure they're sufficient, but they're as practical as they can be. At the end of the day, the responsibility is down to the individual patient it's prescribed to. The doctor has to reinforce the dangers of the drug. That's as happy as you're going to be. The drug clearly has got a role. You can't give every individual capsule to every patient, which is the only way it will be entirely safe."

Erskine supplies thalidomide to about 120 patients a year – 500 to 800 capsules a month. His supply doesn't come from Brazil these days, but from Wales, from a small company called Penn Pharmaceuticals. Penn manufactures the drug to a much higher standard, for which Erskine pays about 75p per pill. Erskine rolls a handful of capsules in his palm; they are off-white and unmarked. The clue lay on the white plastic pot: Sauramide 100mg (Thalidomide). Man. 16/03/95. Ex. 15/03/97.

The patent on the drug has expired, and the molecular structure is available in the textbooks. "I think it's quite a cheap drug to manufacture," Erskine says, "because Penn have no development costs and don't have to do clinical trials. I think they approached us, asking if we thought it was a long-term drug, and would there be a market. We felt there would be."

Penn Pharmaceuticals Ltd lies in the valleys near Merthyr Tydfil, south Wales it looks like an ugly sheet-metal and concrete box on any industrial estate, and it shares its estate with British Steel and a tubing company. The current

construction work at Penn indicates that business is going well, and the photographs of visits by Prince Charles and Prince Andrew in reception suggest the expansion is not going unrecognised.

Roger Jones, the managing director, is 52 and looks a little like Marlon Brando does now. He used to work on the clinical programme at the Wellcome Foundation, but says he left to set up Penn in 1986 because he was frustrated with the slow rate of progress in many trials. He detected a gap in the market for a company that specialised in providing, with greater efficiency, drugs and placebos for patients, as well as bringing all the analytical methods up to speed. "That's Penn's business, our mission."

Jones says he has been interested in thalidomide since he first heard about it in the early Sixties. "I was never convinced that it was a classic teratogen (a drug causing physical defects in a foetus). Many more women had actually taken the drug during the first, critical period than actually gave birth to damaged babies. The fact that they did give birth was a tragedy in every single case, but I would have expected a teratogen to have affected a far larger number of people.

"I was also very curious that the issue had never been resolved legally. The compensation was settled out of court, and I was very curious about that. I believe that there must have been evidence that did not come out, for otherwise why settle?"

Jones surmised that thalidomide interfered with a woman's natural body mechanism for identifying damaged foetuses. He believed that a number of people born with deformities were about the same as you would have naturally have miscarrying in the first trimester. He discussed this with his colleagues at Wellcome, but received little support. "Clinicians are non-iconoclastic," he concluded. "They don't like outrageous suggestions of that kind."

He began making the drug for ulcers, skin grafts and graft-versus-host disease long before the secrets of TNF-alpha and blood vessels were uncovered. Initially, he says, the money he was making from thalidomide wouldn't cover the cost of his petrol. But then HIV pharmacists began calling for it, and researchers began looking at new ways of treating rheumatoid arthritis, and Celgene wanted some help with their formulation.

Jones says that the operating procedure that goes into making his capsules "is mind-blowing". The basic ingredients are common knowledge, but the skill lies in the correct formulation of the five-stage synthesis to ensure good bio-availability (absorption into the bloodstream). He believes that the reason Grünenthal couldn't find a correct level of toxicity was because "the bloody thing wasn't being absorbed".

He will not reveal precisely who he supplies to (beyond saying all the clinical trials are UK-based), nor will he say how many capsules his company currently makes. "Some competitor might quickly work out what the market would be worth and come piling into it. If they want to come into this market, they have to take a risk."

He will admit that his thalidomide production is expanding each year. It used t be that it was just made at weekends, and that all the women who would normally work on the manufacture of other drugs would be asked to leave the production site. "We had very good air-handing results," Jones says, "but I was very concerned that, if there had been any foetal abnormality, then straightaway people would say 'it's your fault', and I really couldn't live with that."

Recently, a suite was designed solely for the men producing thalidomide, which means it can be made all-week round. To enter, one must change twice, into two separate sets of clothing and sterile hats and footwear. One passes through two airlocks. The suite is no larger than a typical double bedroom, and is dominated by two gleaming machines, one a vast mixer, the other a smaller, more complex contraption which Roger Jones asked me not to describe as his competitors copy his methods. In one corner, there are plastic bags of capsule shells. Along one wall there is an automated capsule counter. It's a familiar process to them now: each batch takes a few days.

Jones showed me round the rest of his factory: to the labelling department, the stringent quality control section, the site of the new canteen. He praised the quality of his workforce, and they, indeed, seem a happy crew.

As I left, he repeated what he told me when I arrived – that he believed in the power of thalidomide to do good and improve people's lives. He stressed that it was clearly not immoral to earn money from drugs that make people well. "Remember", he said, "we are the guys wearing the white hats, not the black hats."

In rural Sweden, in the beautiful village of Herrgard, the conversation has turned to Brazil. In November, some of those present at this conference had also attended a meeting near Hamburg. Here, they were addressed by Roseangela Niscimento, president of the Thalidomide Victims Association of Brazil. Niscimento was a first-generation victim like the rest of them, but she told a story of more recent tragedy, of having seen children no more than a few years old who were also born without arms or legs or ears.

"We were absolutely shocked," says Marjolein van Riel, who had travelled to Germany from the Netherlands. "She told us that she had a friend who went to pharmacies in Brazil and just bought the drug over the counter with no problems, saying it was for sister. She brought the drug over to show is, and there was complete silence as it was passed around."

In Brazil, the catastrophe was being played out again, due to ignorance, complacency and greed – the same old reasons. Thalidomide prescribed for the treatment of leprosy was being consumed by pregnant women. Some may have received warnings from their doctors, some may have not; some may have taken drugs prescribed to relatives or friends. In rural areas, it was unlikely that those with leprosy (officially 300,000, but almost certainly many more) had heard of the damage thalidomide could do. Many were illiterate and stricken with poverty. Their drugs often came unlabelled. If they had

heard of the drug, it may have been misinformation: some reportedly took it as a contraceptive; some to hasten abortion.

There are no official figures for the numbers of new thalidomide babies but in 1993 a Yorkshire Television documentary suggested the figure may be more than 1,000. James Cutler, the director-producer of the programme, believes that things have barely improved in the last two years, even though the Brazilian Ministry of Health banned the prescription of thalidomide to women of childbearing age in July 1994. Clearly, there are still many disasters. The photograph of one such Brazilian boy, Raphael, who was born with thalidomide deformities last year and died two months later, was featured in a campaign organised by Hazel Simmonds and Simone Baker, two British thalidomide victims. They urged a mass petitioning of the President of Brazil and the World Health Organisation, calling not for the banning of the drug but for more restricted use, better packaging, and more education for the medical profession.

Again, the impact of the campaign was limited. "We have heard there are still two thalidomide babies being born every week," Simmons says.

A little later, near the pool, Giselle Cole is having a similar conversation. Cole is 34, the secretary of the Thalidomide Victims Association of Canada. She has severely deformed arms because her mother took something for morning sickness. She says: "I would be a very happy woman if this drug could redeem itself in a safe manner. But what infuriates me is the cavalier attitude. They say that, if this drug is shown to do all that people claim it does, then our suffering should be lessened. But you don't know my suffering, or the suffering of my family. There isn't a day when my mother doesn't look at me, and, no matter how successful or independent I've become, she thinks 'if only…'."

Cole says that not too long ago she went in to a casualty department of her local hospital in Ontario. The doctor who examined her said "thali… what?"

"Recently, they've been using the same words to describe the drug as they did in the Fifties: 'Oh, it's a wonder drug – it's so safe'. Greed is a hell of a motivator. To fight the re-licensing takes money, and we don't have it. This is about business, this is not about ethics or morals. The only thing we can affect is what kind of controls they use.

"If this was the cure for Aids or cancer," she concludes, "who wouldn't want that? But there are absolutely safeguards that I can see. People who are terminally ill must do what they must do. But, speaking personally, I would never like to see this drug again."