The third coming

Thalidomide and a final goodbye

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The cyclical rise, fall and resurrection of thalidomide has become one of the most instructive stories in medicine, told most poignantly by Stephens and Brynner[1] in their recent book. In the early 1950s, when pathogens were considered to be the primary causative agents of most human diseases, two chemists working for the pharmaceutical company Chemie Grunenthal heated the peptide pthalimidoglutaramide in an attempt to synthesize novel antibiotics. They obtained a compound with a three-ring structure, which they named thalidomide.

The first coming

Much to their disappointment, thalidomide had no effect as an antibiotic or anti-tumour agent in rats and mice. Large doses of the drug were not lethal in these animals, and the company was impressed by the absence of side effects. Because its structure resembled that of the barbiturates, thalidomide was tested as a sedative in healthy volunteers and was found to be effective. It was then marketed as the safest sleeping pill available and was eventually sold over the counter in 46 European countries. Because of its anti-emetic properties and safety record in animals, pregnant women began to take thalidomide freely as a cure for morning sickness.

The first recorded victim of thalidomide was a girl born without ears in 1956 in Stolberg, West Germany. Her father, who worked for Chemie Grunenthal, had given free drug samples to his pregnant wife. Soon thereafter, a striking increase was noted in the number of infants with developmental abnormalities, especially those born with hands and feet attached to the body, without arms or legs. In addition, up to 20% of adults taking thalidomide began to show nerve damage. Before a full appreciation of the scope of thr medical catastrophe and eventual withdrawal of thalidomide, some 40,000 people had suffered from peripheral neuritis and 12,000 infants were deformed by thalidomide. These infants eventually became known as thalidomiders and approximately 5000 of them survived past childhood.

Richardson-Merrell Inc. had bought the rights to market thalidomide in the USA, but thanks to the vigilance of Frances Kelsey who carefully reviewed the application for the Food and Drug Administration (FDA), it was never approved for use. She hypothesized that the lack of side effects in animals could be the result of non-absorption and therefore data from such studies would not be applicable to humans. She was awarded the President's Award for Distinguished Federal Civilian Service in 1962 for her courageous stand against pressure from many sources.

The second coming

In 1964, Jacob Sheskin, while working with lepers in Jerusalem, had an extremely debilitated patient who suffered from erythema nodosum leprosum (ENL), who had been unable to sleep owing to severe pain. In his medicine cabinet, Sheskin found an old bottle of thalidomide and, with nothing to lose, administered the drug to the patient, who after two tablets slept better than he had in months. After another two tablets the following night, his lesions began to heal and Sheskin knew that this could have important implications. He treated another half a dozen ENL patients with similar dramatic results, and a larger World Health Organization (WHO) study, which included thousands of lepers in 52 countries, showed that 99% of patients had total remission of the disease within a couple of weeks of treatment with thalidomide.

How and why did this happen? Despite the medical catastrophe associated with thalidomide, this drug never completely disappeared, and it received FDA approval for the treatment of ENL in the USA in 1998. An intense investigation into its mechanism of action commenced, followed by an unprecedented excitement in the medical community as it became apparent that this drug could be useful in the treatment of a number of conditions where the pathology involved neo-angiogenesis, immune dysregulation and mediation of symptoms by the pro-inflammatory cytokine tumour necrosis factor (TNF).

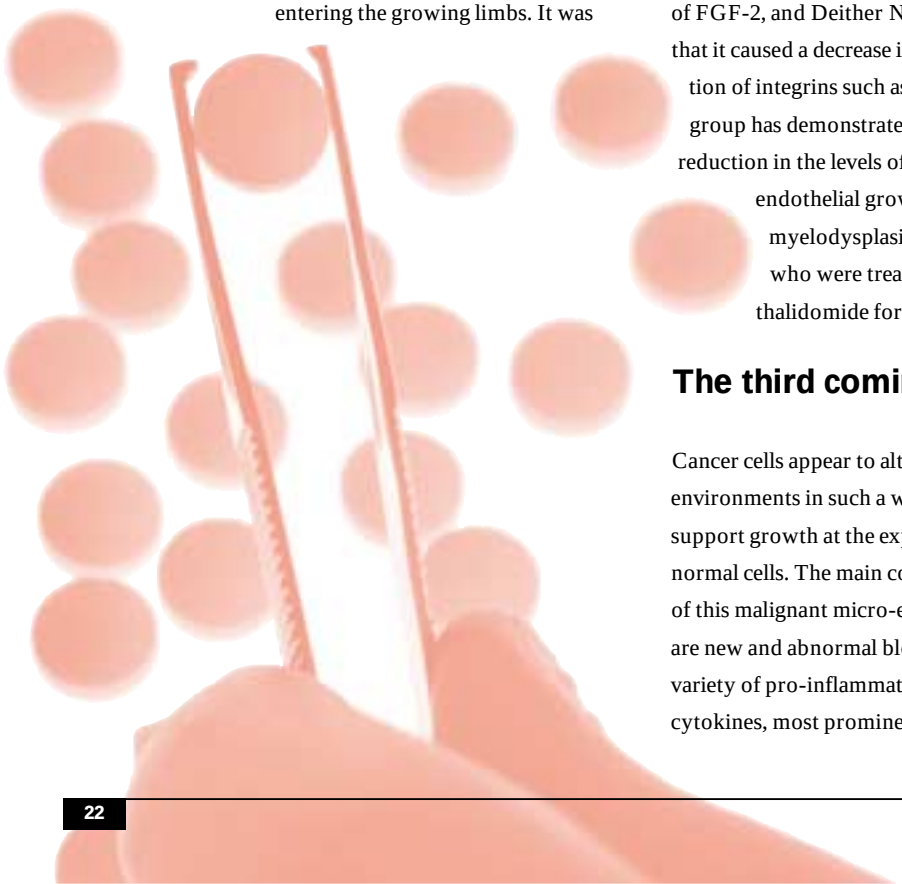
Mechanism of action

In 1991, Gilla Kaplan of Rockefeller University in New York showed that TNF levels were very high in the blood and lesions of leprosy patients, and that thalidomide reduced these levels by as much as 70%. Selective

thalidomide-mediated suppression of TNF production by monocytes and macrophages diminished the inflammatory reaction in ENL, thereby preventing secondary, end-organ damage. Thalidomide causes healing in lesions of pyoderma gangrenosum by a similar anti-TNF mechanism. The teratogenic effects, which can occur following the ingestion of one tablet of thalidomide at the wrong time during pregnancy, proved far more difficult to explain. More than two dozen mechanisms have been proposed to explain how thalidomide prevents limb development. Janet McCredie observed that bone loss in limbs follows patterns of innervation, suggesting that bone loss resulted from reduced nerve supply. When applied to the foetus, this would equate peripheral neuropathy in adults taking thalidomide with nerve damage in the growing embryo, thereby preventing skeletal development. However, this theory was abandoned when Trent Stephens[2] elegantly demonstrated that the limb skeleton developed normally despite foil barriers implanted in chick embryos to prevent nerves from entering the growing limbs. It was postulated that thalidomide may prevent formation of new blood vessels that are essential for delivery of nutrients to the growing limbs.

The possible mechanism by which thalidomide exerts this anti-angiogenic effect has recently been suggested by Stephens[2]. A part of the thalidomide molecule resembles adenine and guanine, which gives it a special affinity for guanine, and some for adenine. Because of this structural similarity, thalidomide can intercalate into DNA. Genes for several angiogenic factors, such as fibroblast growth factor 2 (FGF-2), insulin-like growth factor 1 and $\alpha v\beta 3$ integrin (avb3), have promoters rich in GGGCGGG motifs, which interact with Sp1 binding proteins to initiate transcription. If thalidomide intercalates preferentially in these sites and diminishes the transcription of each of these genes by even a fraction, the combined effect would be sufficient to halt angiogenesis and arrest limb development.

Robert D'Amato and Judah Folkman[3] showed that thalidomide exerts its anti-angiogenic effects by down-regulating the production of FGF-2, and Deither Neubert found that it caused a decrease in the production of integrins such as avb3. Our group has demonstrated a marked reduction in the levels of vascular endothelial growth factor in myelodysplasia patients who were treated with thalidomide for 12 weeks.



The third coming

Cancer cells appear to alter micro-environments in such a way as to support growth at the expense of normal cells. The main components of this malignant micro-environment are new and abnormal blood vessels, a variety of pro-inflammatory cytokines, most prominent being TNFa, and immune regulatory cells, some of which are the source of the cytokines.

A novel approach to treat cancers, based on targeting various components of the micro-environment that support the malignant cells rather than the cancer cells directly, has been evolving over the last decade. An interesting observation has been that primary tumours in mice can attain large sizes without producing metastases. The removal of a primary tumour, however, results in a shower of rapidly growing metastases. In 1971, Folkman proposed that tumours depend on neoangiogenesis for their primary growth and metastases, and that primary tumours must produce an inhibitor of neoangiogenesis to keep metastatic lesions dormant. Removal of the primary tumour eliminates the anti-angiogenic agent, allowing the dormant metastases to blossom. He was eventually proved to be correct when Michael O'Reilly successfully isolated 'angiostatin' from mice bearing Lewis lung cancer, and showed that angiostatin was actually plasmin[4], a protein that is normally produced in our bodies by the truncation of the larger protein plasminogen and that is involved in fibrinolysis.

A second anti-angiogenic protein, endostatin, has since been isolated and recombinant angiostatin and endostatin have already been used to treat a variety of human malignancies in phase I studies. This exciting research fuelled the drive to identify other agents with anti-angiogenic potential. Robert D'Amato (in Judah Folkman's lab) was the first to demonstrate the anti-angiogenic activity of thalidomide. In addition, thalidomide is both a potent suppressor of TNFa and an immune-modulator, thereby making it an ideal drug with a broad spectrum of activity against all three major components of the micro-environment.

A patient suffering from multiple myeloma (MM), a haematological malignancy which demonstrates evidence of increased marrow vasculature, was advised by Folkman to take thalidomide. Although the patient himself did not benefit from the drug, Singhal et al.[5] demonstrated that other MM patients showed unexpectedly positive responses to thalidomide treatment. Our group has been investigating another haematological malignancy, the pre-leukaemic disorders called myelodysplastic syndromes (MDS). In these diseases, patients present with cytopenias in the face of cellular marrows, and a third of them develop acute myeloid leukaemia (AML). We found that MDS marrows have more cells in S-phase and that their cell cycles are shorter than normal or AML marrows. Thus, it is not a disease of marrow failure; if anything, the marrow appears to be in 'hyper-drive'. Failure of haematopoietic cells to reach the blood was then shown to be caused by excessive, cytokine-mediated apoptosis in the marrow; the primary pro-apoptotic cytokine turned out to be none other than TNFα. In addition, there is evidence of enormous increase in marrow microvessel density in MDS patients.

Finally, there appears to be an inherent immune defect in these diseases since the marrow is frequently infiltrated by lymphocytes and plasma cells, despite a T-cell cytopenia. Thalidomide is a highly suitable drug for these patients because of its anti-TNF, anti-angiogenic and immune system modulating properties[6]. In fact, a trial of 83 patients with MDS was completed earlier this year, and it was found that approximately 30% of the patients who could tolerate the drug at daily doses of 100–200 mg responded to the drug, and the majority changed from being heavily transfusion-dependent to being transfusion-independent[7]. In addition to these two haematological diseases for which thalidomide has proved effective, reports are appearing regularly that demonstrate its efficacy in other malignancies such as low-grade lymphomas, AML, renal and prostate cancers. Thus, thalidomide has made its third comeback.

Photos courtesy of Photodisc

Final goodbye

Despite the proven efficacy of thalidomide in the treatment of such varied diseases as leprosy, cancers and pyoderma gangrenosum, there is a nagging concern that somehow another pregnant woman will take it inadvertently and the tragedy of another thalidomider will occur. Celgene Corporation, the makers of thalidomide, have done an outstanding job of trying to assure patient education and safety by putting in place a programme called S.T.E.P.S.[8]; yet the possibility of accidental ingestion cannot be entirely eliminated. Obviously, it would be very satisfactory if a substitute for thalidomide was found which preserved its efficacy but had none of the toxicity.

Celgene has now manufactured two analogues of the drug that are several thousand times more effective than the parent compound, but without the side effects. One of these agents, compound CC-5013, has been shown to be effective in MM patients, and the other, compound CC-1088, is being used in the treatment of MDS. If these agents live up to their promise in the clinical setting, then a resounding goodbye can finally be said to thalidomide. As the thalidomider Randy Warren says poignantly, "When that day comes, all those involved in the suffering can gather together for thalidomide's funeral."

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