

**FORGIVE SINS: RISE OF THALIDOMIDE**

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**Abstract**

Thalidomide was originally used as a Wonder Drug to treat morning sickness and insomnia in pregnant women in late 1950s. It became apparent in early 1960s that thalidomide treatment resulted in severe birth defects in thousands of children. Then it was banned in most of countries. Later on discovered anti-inflammatory and anti-angiogenic properties of Thalidomide proved to be useful for treatment of leprosy and multiple myeloma. A series of immunomodulatory drugs created by chemical modification of thalidomide have been developed to overcome the original devastating side effects. It's being investigated extensively as a treatment for many other severe cutaneous disorders and advanced cancers.

We briefly review pharmacological and the therapeutic profile of thalidomide.

**Key words:** Amelia; Contegran; ENL; Phocomelia; Teratogenetic defects; Thalidomide.

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**Introduction**

Thalidomide is a synthetic glutamic acid derivative was synthesized in 1954, by Chemie Grunenthal under the brand name of Contegran and was subsequently licensed in 46 other countries worldwide, covering all continents. It is an odourless white crystalline compound with low solubility in water [1-3]. We briefly review here pharmacological, therapeutic properties and side effects of thalidomide in Dermatology.

**History**

Thalidomide is potent hypnotic, antiemetic and used as a Sedative. Because of as an antiemetic, thalidomide was often administered on pregnant women [1].

It became an attractive alternative to barbiturates in view of its rapid speed of onset, lack of hangover effect and apparent safety after overdose [4,5].

Dr. Heinrich Muckter accidentally identified sedative property of thalidomide in 1954. The drug was first marketed in Germany in 1957 under the name Contegran [1], and in the UK in April 1958 as Distaval. Later, compound preparations which combined thalidomide with other drugs were marketed for a wide variety of indications: Asmaval for asthma, Tensival for hypertension, Valgraine for migraine, and so forth.

However, soon after its release, there was a marked increase in cases of phocomelia (congenital limb foreshortening). In 1961,

after reports linking this to in-utero thalidomide exposure, the drug was withdrawn leaving a legacy of about 10,000 affected children [5].

In November 1961, Lenz suggested that these deformities resulted from the mothers having taken thalidomide. By a remarkable coincidence, the same suggestion was made at much the same time by McBride [3] in Australia.

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).

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 of taken only after the 50th day [3].

Within the sensitive period from day 35 to day 49 there is the following sequence [3]:

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.

About 40 per cent of thalidomide victims died before their first birthday. Thalidomide was withdrawn in Germany by the end of November 1961 and In Japan, it was finally withdrawn in September 1962.

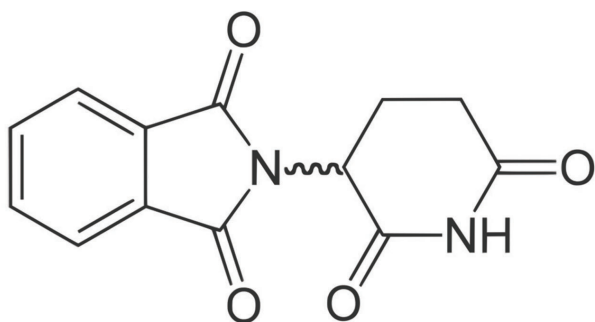
Sheskin, an Israeli physician, administered some old supplies of thalidomide to his patient with mania and leprosy for inducing sleep. There was a dramatic and complete resolution of the patient's cutaneous symptoms and Sheskin published this in 1965. This observation maintained the interest in thalidomide and it was soon obvious that the drug has important contribution in the treatment of erythema nodosum leprosum.

In 1997, however, the Food and Drug Administration (FDA) allowed thalidomide to be used on erythema nodosa leprosum (ENL), largely thanks to Sheskin's work in 1965 [4].

In 1991, thalidomide's anti-tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) activity was discovered and this virtually intensified the interest in the potential uses of this unique drug [5]. Currently it is being evaluated or used on a compassionate use basis in more than 30 conditions including dermatologic, infectious, autoimmune and malignant disorders.

### Pharmacology

Thalidomide is a nonpolar synthetic glutamic acid derivative. Chemically, it is an  $\alpha$ -[N-phthalimido]-glutarimide consisting of a single central asymmetric carbon atom with a left phthalimide ring and a right glutarimide ring. The phthalimide ring is thought to be responsible for the teratogenic effects whereas the glutarimide ring, which is structurally similar to other sedatives, mediates sedation. It exists as optically active R (+) and S (-) enantiomers, which interconvert rapidly in vivo [4] (Fig. 1).



**Figure 1.** thalidomide are aromatic polycyclic compounds, contain one isomer responsible for treating morning sickness, another isomer responsible for Teratogenic effects. Chemical formula is C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>.

### Pharmacokinetics

Thalidomide is slowly absorbed from the gastrointestinal tract. Peak levels in blood are reached within 2–6 hours, which could be delayed with a high-fat meal. It is extensively distributed in all the tissues and fluids with higher concentrations in skin and kidneys. Bioavailability of thalidomide cannot be ascertained owing to its poor water solubility. It is primarily metabolized by nonenzymatic hydrolytic cleavage of its amide bonds. Cytochrome P-450 enzymes may have some role in metabolizing the anti angiogenic metabolite [4]. The mean elimination time is 5-7 hours, and it is not excreted in renal system; less than 0.7 percent of the drug is found in the urine [2,6].

### Mechanism of Action

The exact mechanism of thalidomide actions is not determined. However, various theories have been proposed.

### Anti inflammatory

It inhibits the chemotaxis, phagocytosis by Neutrophils, lymphocytes, and macrophages, stabilizes the lysosomal membranes and decreases the generation of superoxide and hydroxyl radicals [1,4].

### Anti tumour effects

Thalidomide has been tested in a variety of haematological and solid malignancies. It has shown remarkable efficacy in patients with advanced multiple myeloma [17]. The exact basis for thalidomide's anti-tumour activity is not well-understood. It may be related to its anti angiogenic action, immunomodulatory effects, TNF- $\alpha$ -regulation, effect on cytokines and anti-adhesion effects.

### Immunomodulatory effects

Thalidomide's immunomodulatory properties are complex. Multiple mechanisms of action have been reported. The best recognised action is its ability to inhibit the production of TNF- $\alpha$ , inhibit synthesis of IL-6, IL-12 and interferon- $\gamma$  (IFN- $\gamma$ ). It reduces expression of intracellular adhesion molecule-1 and vascular cell adhesion molecule [5].

### Anti angiogenesis

Many tumours require new vessel formation (angiogenesis) in order to support their continuous growth. Thalidomide inhibits basic fibroblast growth factor (bFGF) (induces angiogenesis) and vascular endothelial growth factor (VEGF) [4-6]. Thalidomide-induced antiangiogenic action is mediated by ceramide through depletion of VEGF receptors [7,17]. Angiogenic inhibition also results from antagonism between the following elements: E2 and F2 prostaglandins, histamine, serotonin and acetylcholine [1].

### Sedative properties

It activates the forebrain sleep centre and therefore does not cause respiratory depression, in coordination, or hangovers [4].

### Miscellaneous Actions

Thalidomide Reduces cellular proliferation, myelin phagocytosis and subperineural oedema. There is decrease in the capacity to release elastase and lactoferrin by lipoteichoic acid-stimulated granulocytes granulocytes [8].

### Indications

In Table I was described therapeutic uses of Thalidomide and in Table II Contraindications.

### Uses in Dermatology

Dermatological conditions have been grouped into the following categories:

- Very effective: ENL, aphthous stomatitis, Behcet's disease, LE, and prurigo nodularis;
- Moderately effective: Actinic prurigo, Langerhans cell histiocytosis, cutaneous Sarcoidosis, erythema multiforme, graft-vs.-host disease (GVHD), Jessner's infiltrate, and uremic pruritus;
- Possibly effective: Kaposi's sarcoma, lichen planus, melanoma, and pyoderma gangrenosum;
- Contraindicated: Toxic epidermal necrolysis (paradoxical increase in TNF- $\alpha$  activity).

	List of Therapeutic Uses		List of Therapeutic Uses
A	<b>Autoimmune disorders:</b> * Rheumatoid arthritis * Systemic lupus erythematosus * Discoid lupus erythematosus * Sjögren's syndrome * Sarcoidosis * Multiple sclerosis	E	<b>Miscellaneous:</b> * Graft versus host disease * Neuropathic pain * Diabetic retinopathy * Macular degeneration
B	<b>Gastrointestinal:</b> * Recurrent aphthous oral ulceration * HIV associated oral and oesophageal ulceration * Crohn's disease	F	<b>Haematological malignancies:</b> * Multiple myeloma * Myelodysplasia * Myelofibrosis with myeloid metaplasia
C	<b>Dermatological:</b> * Leprosy * Behçet's disease * Actinic prurigo * Prurigo nodularis * Uraemic pruritus * Pyoderma gangrenosum	G	<b>Solid tumours:</b> * Malignant glioma * Kaposi's sarcoma * Prostatic carcinoma * Colorectal carcinoma * Renal cell carcinoma * Carcinoma of breast
D	<b>Cachexia and weight loss:</b> * Cancer cachexia * HIV-associated wasting * Tuberculosis associated wasting		

**Table I. Therapeutic indications of Thalidomide.**

List of contraindications
<ul style="list-style-type: none"> <li>· accidental exposure</li> <li>· blood donation</li> <li>· breast-feeding</li> <li>· children</li> <li>· driving or operating machinery</li> <li>· dysfunctional uterine bleeding</li> <li>· females</li> <li>· human immunodeficiency virus (HIV) infection</li> <li>· intrauterine fetal death</li> <li>· leukopenia</li> <li>· TEN</li> </ul>

**Table II. Contraindications of thalidomide.**

The only FDA-approved indication for thalidomide is the acute treatment and suppression of the cutaneous manifestations of erythema nodosum leprosum (ENL). Rest of indications are off-labeled dermatological uses.

#### **Erythema nodosum leprosum (ENL)**

ENL is a lepra reaction that occurs in lepromatous patients on multiple drugs or from interferon- $\gamma$  (IFN- $\gamma$ ) intradermal injections. It usually presents within the first year of multidrug therapy with both cutaneous and visceral manifestations. Skin reactions are erythematous nodules associated with arthralgia, fever, iritis, malaise and neuritis. Visceral manifestations can include hepatosplenomegaly, nephritis, orchitis and pleuritis [8].

It is both a cell-mediated immune response as well as an immune complex mediated disease. Patients have raised INF- $\gamma$ , TNF- $\alpha$  and IL-12. Thalidomide's effectiveness is due to its anti-cytokine properties. After therapy, there is marked reduction

in TNF- $\alpha$  along with down regulation of intracellular adhesion molecule-1 [2].

The response rates for thalidomide have been greater than 90 percent, with improvement seen within days and complete resolution within 2 weeks. The other symptoms of ENL also responded rapidly. The most common side-effects were somnolence and constipation [6,8]. Although thalidomide is considered first-line for ENL, no trials have compared it with corticosteroids or clofazimine [8].

Sheskin reviewed 4522 patients treated with thalidomide for ENL, and found that 4479 (99%) improved while only 43 (1%) had no change or worsened. The best initial dose seemed to be 400 mg daily, with a maintenance dose of 50–100 mg daily. The duration of therapy ranged from sporadic use to continuous use for greater than 6 years [8].

In Parikh et al study, where the dosing solely depended on the clinical response of the patient.

They started thalidomide at 100 mg four times a day and then the dose was reduced to thrice, twice and once per day depending on the patient's clinical improvement. The duration of this study ranged from 12 to 643 days and the maintenance dose was 50 mg/day [10,11]. The recommended dosage is to begin with 100-400 mg at night and continue with this dose until the symptoms subside. Thereafter, tapering by 50mg every 2-4 weeks is recommended. Patients can be maintained on 25-200 mg a day to prevent an ENL recurrence [6,10].

### **Lupus Erythematosus**

The first reported successful thalidomide treatment of chronic cutaneous lupus erythematosus (CCLE) was in 1977 in a case series of 20 patients. One large clinical trial of 60 patients with CCLE reported complete or marked responses in 54 patients (90%), but 71% of patients relapsed after discontinuing treatment.

Patients with relapse again responded when therapy was reinitiated [2,8].

Pelle and Werth reviewed 8 separate case series that reported a total of 171 patients with various forms of cutaneous lupus treated with thalidomide. The overall response rate was 85%, with complete resolution in 59%; the response rates for discoid lupus erythematosus and subacute cutaneous lupus erythematosus were comparable at 90.3% and 82.4%, respectively [2].

Thalidomide has also been used to effectively treat refractory tumid lupus erythematosus [2,9], but the drug has not been as successful in treating lupus panniculitis [2]. Coelho and colleagues reported a complete or partial response in 99% of patients with all types of cutaneous lupus treated with thalidomide (100mg daily tapered to 50mg daily or less when clinically feasible). Two thirds of patients with lupus panniculitis, however, had no response to treatment [2].

### **Apthous stomatitis**

The first report of thalidomide for recurrent apthous stomatitis was in 1979. Six patients had scrotal and mouth ulcers and were treated with thalidomide 100mg daily. The lesions were painless after 2-3 days and completely resolved after 7-10 days. Thalidomide is also beneficial for human immunodeficiency virus (HIV)-associated apthous ulcers [8].

One mechanism by which thalidomide works in apthous stomatitis is by inhibiting the increased chemotactic response of Neutrophils [6].

### **Behcet's syndrome**

Behcet's disease is a systemic disorder with various skin lesions, ocular disease (panuveitis), arthritis, intestinal bleeding, and recurrent apthous orogenital ulcers.

After successful reports of the efficacy of thalidomide in treating apthous ulcers, thalidomide was used for Behcet's syndrome. Thalidomide was given at 400mg daily for the first 5 days, followed by 200mg daily for the next 15-60 days. Oral and genital lesions healed very rapidly, with milder and shorter recurrences.

Thalidomide may work in Behcet's syndrome by reducing the production of hydroxyl and superoxide radicals that cause tissue damage at sites of inflammation [12,14].

### **Prurigo nodularis**

Prurigo nodularis is a pruritic type of neurodermatitis with

skin-colored, erythematous, or hyperpigmented cutaneous nodules. Patients with Prurigo nodularis can be difficult to treat, and standard therapies with corticosteroids and antihistamines may be ineffective.

The initial report of thalidomide's efficacy in treating Prurigo nodularis was in 1965 by Sheskin. A more recent retrospective study presented 12 patients with Prurigo nodularis who were given thalidomide for at least 1 month at an initial dosage of 100mg daily. Response was noted in 8 of 12 patients, ranging from mild to moderate improvement, with complete resolution in 1 patient [2].

Several theories have been proposed about the mechanism of thalidomide in prurigo nodularis. Thalidomide may have a local effect on proliferated neural tissue in prurigo nodularis. A central effect of thalidomide may be the secondary peripheral neuropathy (to lose the sensation to scratch) and the sedation. The sedative properties of thalidomide may disrupt the itch-scratch cycle [8].

### **Actinic prurigo**

In a study 1970, 34 patients treated with thalidomide and obtained good results in 30 cases over a period varying from one to two months. There was recurrence of the condition after the drug was halted. This was also confirmed by other authors. actinic prurigo also may require ongoing, maintenance drug to prevent relapse of disease [2].

### **Graft-versus-host disease**

The case reports and clinical trials have not been conclusive, as some demonstrate efficacy while others do not. Thalidomide has shown beneficial effects in both acute and chronic forms of graft-versus-host disease [15].

Chao et al. performed a randomized, double-blind, placebo-controlled study with 59 patients to evaluate the efficacy of thalidomide as a prophylactic agent in the prevention of chronic GVHD. The treatment group received 200mg of thalidomide twice a day beginning 80 days following allogeneic bone-marrow transplantation. The treatment group actually developed chronic GVHD more often than the placebo group. A recent study showed that thalidomide can be beneficial in the treatment of chronic GVHD in patients refractory to prednisone and cyclosporine [6].

### **Sarcoidosis**

The treatment with thalidomide (200mg daily for two weeks, followed by 100mg daily for 11 weeks) improved the cutaneous lesions, hilar lymphadenopathy and Kaposi's sarcoma [1,17].

Sarcoidosis involves a Th1-type immune response characterized by increased levels of interferon- $\gamma$  (IFN- $\gamma$ ), interleukin (IL)-2, and IL-12. Also, tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) plays a major role by escalating macrophage recruitment into granulomatous lesions [2]. This response was attributed to macrophage inhibition. No benefit attributed in treatment of Pulmonary Sarcoidosis [13].

### **Langerhans cell histiocytosis (histiocytosis X)**

There are various reports on thalidomide's therapeutic effect here, but treatment doses and time have fluctuated according to various authors. In many instances, however, patients relapsed after cessation of treatment and ultimately required maintenance dosages [1,6].

### **Jessner's lymphocytic infiltrate**

Guillaume studied 28 patients. Thirteen patients received thalidomide and 15 placebos. Of the 13 treated, 11 had remission where as the 15 who received the placebo showed no improvement [1].

### **Lichen Planus**

Thalidomide has been used in the treatment of lichen planus, but only case reports exist. TNF- $\alpha$  has been implicated in mediating the effects of lichen planus, so thalidomide's ability to suppress this cytokine has led to its use in this disease [6]. In a 25-150 mg daily dose, thalidomide produced a regression of the oral lichen planus lesions with in 4 months of treatment [1].

### **Cicatricial Pemphigoid**

There has been limited experience, just a small series and a case report have been published. Duong et al. reported the use of thalidomide in a patient with cicatricial pemphigoid, an autoimmune blistering disorder affecting the mucous membranes and occasionally the skin. Cicatricial pemphigoid is usually treated with dapsone or immunosuppressants. Because the patient's oral and cutaneous lesions had not responded to these treatments, he was treated with 100mg of thalidomide a day and improvement was noted after just 5 months. The disease remained stable after a taper of the thalidomide [6].

### **Pyoderma gangrenosum**

Pyoderma gangrenosum is a non-infectious skin disorder that begins as painful pustules or papulonodules that enlarge and ulcerate. Several case reports have reported thalidomide's effectiveness in Pyoderma gangrenosum unresponsive to other treatments. One recent case of Pyoderma gangrenosum related to myelodysplastic syndrome had dramatic improvement of massive ulcerovegetative lesions after 4 months of combination therapy with IFN-  $\alpha$ 2 a and thalidomide (200mg daily) [2]. Farrell and cols. treated two cases with corticosteroids and minocycline. One of latter associated with thalidomide in a 100mg daily dose for five days, with an improvement of the condition [1].

### **Necrobiosis lipoidica**

A case of necrobiosis lipoidica that was unresponsive to therapy was treated with thalidomide (150mg daily). Four months after initiation of therapy, there was clinical improvement in all lesions, and thalidomide was tapered to 50mg daily.

### **Postherpetic neuralgia**

Treatment with thalidomide is effective, although with recurrence three weeks after halting the drug [1].

### **Erythema multiforme**

Various cases were treated with thalidomide (100mg daily), showing good results, but with posttreatment recurrence [1].

### **Uremic Pruritus**

For uremic patients receiving hemodialysis, pruritus occurs in 80% to 90% of patients at some point. The cause remains unclear, and no standard treatments have yet been established. In a crossover, randomized, double-blind trial, thalidomide (100mg daily for 7 days) was compared with placebo for treating refractory uremic pruritus in 29 patients. Of 18 patients finishing the study, approximately 55% showed

a response to thalidomide whereas none responded to placebo. Although promising, additional investigation is needed to evaluate thalidomide's efficacy for management of uremic pruritus [2].

### **Human Immunodeficiency Virus**

HIV has been treated with thalidomide because it does have some proven anti-retroviral effects associated with its inhibition of TNF- $\alpha$  production. TNF- $\alpha$  stimulates a cellular transcription factor that induces the expression of HIV from chronically infected cell lines [16]. Blocking of TNF- $\alpha$ - stimulated HIV replication by thalidomide has been demonstrated both in vitro and ex vivo [6].

### **Wasting and cachexia**

Thalidomide has been shown to retard or reverse the weight loss associated with a number of conditions i.e. HIV infection, active pulmonary tuberculosis and advanced malignancies. Cachexia, in these disorders, is mediated through a Th1 immune response with increased production of TNF- $\alpha$ , IL-1 $\beta$  and IL-6, all of which are reversed by thalidomide [1].

### **Toxic epidermal necrolysis**

The pathogenesis of toxic epidermal necrolysis was believed to be related to an increased level of TNF-  $\alpha$  [8]. 12 patients were treated with thalidomide (400mg daily for five days). However, 10 had a lethal outcome. In the 10-patient placebo group, three died [1]. This is not a good indication for the therapeutic use of thalidomide. Thalidomide is known to be a powerful inhibitor of TNF-  $\alpha$ .

### **Adverse effects**

Common adverse effects reported during treatment with thalidomide are summarized in Table III. Common side-effects are sedation and constipation. The degree of sedation decreases with continued administration at a constant bedtime dosing. Fortunately, any 'hang-over' effect is minimal. Constipation is a significant problem with doses around 400 mg/d or more. The most serious adverse effect is teratogenicity.

### **Teratogenicity:**

Thalidomide's most severe toxicity is teratogenicity. This agent should never be used by pregnant women or anyone who could become pregnant, because it is labeled pregnancy category X.

Severe birth defects can result from only a single dose of thalidomide, with teratogenic risk at its highest during the critical period of 35 to 50 days after the last menstrual period. It has become possible to delineate wide spectrum of malformations attributable to the drug [3,6] (Fig. 2A - D).

#### These were:

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

Amelia totalis: Complete absence of four limbs.  
 Phocomelia: Arm, forearm in upper limb and thigh, leg absent in lower limb. So hands and feet sprout directly from trunk.  
 Ectrocheiria: Total or partial absence of hand.  
 Ectromelia: Total or partial absence of fingers or toes.  
 Ectrophalangia: Absence of one or more phalanges.

Ectropodia: Total or partial absence of foot.  
 Hemimelia: Absence of one of the paired bones of limbs.  
 Polydactyly: Presence of Extra digits.  
 Syndactylyl: Fusion of fingers.  
 Oligodactyly: Presence of fewer fingers or toes less than five.

	List of Adverse effects		List of Adverse effects
A	<b>Teratogenicity:</b> * A single dose of 50mg is adequate to produce serious defects	E	<b>Macular rash:</b> * Self-limiting on stopping treatment * More common in HIV-positive patients
B	<b>Peripheral neuropathy:</b> * Predominantly sensory * Axonal degeneration * Occasionally permanent	F	<b>Neutropenia:</b> * Rare * More common in HIV-positive patients
C	<b>Somnolence:</b> * Virtually universal * Administer at bedtime to reduce effect * Tolerance develops	G	<b>Miscellaneous:</b> * Xerostomia * Weight gain * Oedema of face / limbs * Decreased thyroid hormone production * Hypotension
D	<b>Constipation:</b> * Occasionally severe * Laxatives commonly needed		

Table III. Adverse effects of Thalidomide.

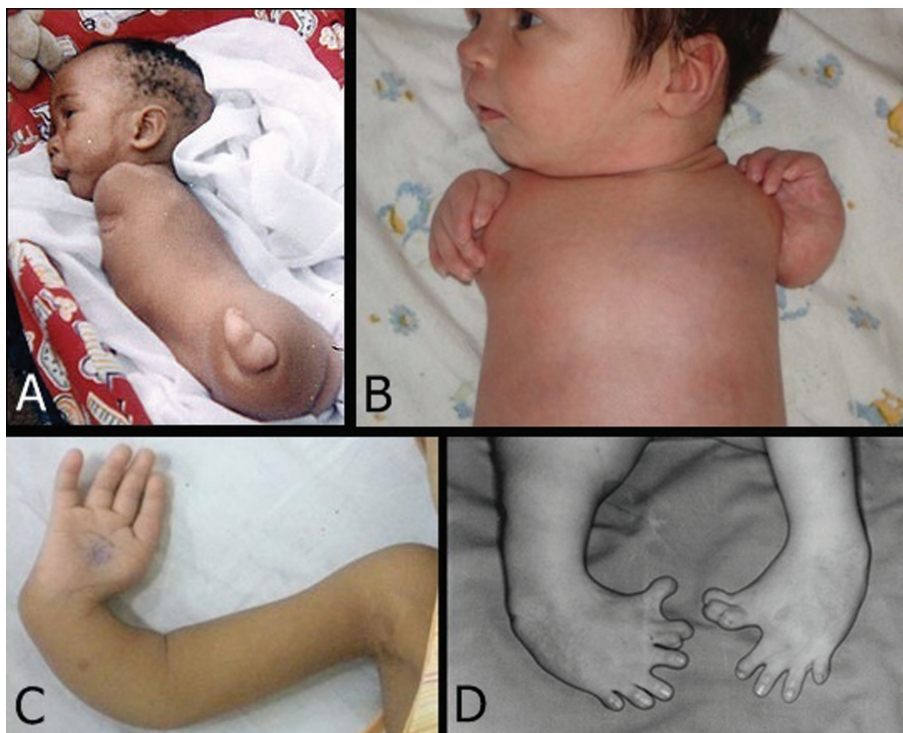


Figure 2A. Bilateral Complete Absence of upper and lower limbs. (Amelia totalis) (Courtesy of [www.news.bbc.co.uk](http://www.news.bbc.co.uk)); B. Absence of arms and forearms. (Phocomelia) (Courtesy of [www.duke.edu](http://www.duke.edu)); C. Absence of thumb, shortening of distal end of radius, angulation of radius bone i.e. radial club hand. (Courtesy of [www.medibird.com](http://www.medibird.com)); D. Presence of Multiple fingers (Polydactyly). Fusion of digital fingers (Syndactyly) (Courtesy of [en.wikipedia.org](http://en.wikipedia.org)).

They are also readily prevented by taking precautions and following guidelines for avoiding pregnancy while on thalidomide. Due to teratogenic potential, the manufacturer requires all physicians prescribing thalidomide to follow the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.). Thalidomide can be prescribed for only 28 days at a time with no refills. Prescriptions are valid for 1 week only, and monthly pregnancy tests are required [2].

### Peripheral Neuropathy

Thalidomide may cause irreversible peripheral neuropathy presenting as symmetric painful paresthesias of extremities with sensory loss in the lower extremities with or without muscle cramps or weakness. Electrophysiologic findings show an axonal neuropathy with reduced sensory nerve action potentials, and loss of large-diameter nerve fibers without segmental demyelination is seen on biopsy [4].

There was a significant correlation between neuropathy and cumulative doses for patients receiving more than 20g of thalidomide. The severity of neuropathy was also dose related for this group. For patients given less than 20g, neuropathy occurred less often [2].

### Thromboembolic effects

Thromboembolic complications due to thalidomide are mostly associated with thalidomide's use in the cancer setting, especially when given concomitantly with chemotherapeutic agents [2]. Venous thromboembolism has emerged as the single most important complication of thalidomide in the setting of malignancy especially multiple myeloma. Venous thromboembolism was noticed in less than 5% of advanced myeloma patients taking thalidomide as a single agent [5].

It is also an emerging toxicity of thalidomide in the dermatologic setting, however. There are at least 15 cases of thalidomide-related thromboses in the noncancer setting, including among cases of sarcoidosis, lupus erythematosus, and atopic dermatitis. The risk increases when thalidomide is combined with corticosteroids (such as dexamethasone). It may be advisable to screen patients for possible thrombotic predisposition before thalidomide treatment [2].

### Thalidomide derivative

Thalidomide analog includes lenalidomide (phase-II and -III clinical trials), revimid, and actimid, and are very potent in the treatment of multiple myeloma and other oncologic conditions.

### Conclusion

Thalidomide is a double-edged weapon. After thalidomide use, it was prohibited due to its teratogenic effects (SINS). The 1961 tragedy remains as a bitter lesson in our minds and serves as a reminder to exercise extreme caution and vigilance when using any new drug. Anyone using thalidomide should follow the S.T.E.P.S. program and closely monitor for side effects in treated patients. Thalidomide should be considered when the underlying conditions are disabling or disfiguring and recalcitrant to other therapies. Thalidomide attracting growing interest because of Anti inflammatory and Immunomodulatory effects. Despite the

major drawbacks of thalidomide - teratogenicity and peripheral neuropathy, now it has been administered for diverse dermatoses with relative success where standard anti inflammatory or immunosuppressive therapies have failed. So we described it a title name, "FORGIVE SINS OF THALIDOMIDE: RISE OF INDICATIONS OF THALIDOMIDE IN DERMATOLOGY".

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