

Potential Novel Uses of Thalidomide

Focus on Palliative Care

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Abstract

Thalidomide, after being banned from the market in the early 1960s because of the worldwide teratogenesis disaster, is currently being rediscovered because of its multiple therapeutic effects in various serious diseases and symptoms. Original studies examined the anxiolytic, mild hypnotic, anti-emetic and adjuvant analgesic properties of this drug. Subsequently, thalidomide was found to be highly effective in managing the cutaneous manifestations of leprosy (erythema nodosum leprosum) and even to be superior to aspirin (acetylsalicylic acid) in controlling leprosy-associated fever. Recent research shows promising results with thalidomide in patients with progressive bodyweight loss related to advanced cancer and HIV infection. Thalidomide therapy of diseases such as tuberculosis, sarcoidosis, aphthous ulcers in HIV syndrome and Behcet's disease, rheumatoid arthritis, multiple myeloma, graft-versus-host disease, pyoderma gangrenosum, inflammatory bowel disease, Sjögren's syndrome, lupus erythematosus and a variety of solid tumours is currently being explored.

Furthermore, in preliminary studies, thalidomide has been found to be effective in several syndromes related to advanced cancer, such as the cancer cachexia syndrome, chronic nausea, insomnia, profuse sweating and pain. Whether thalidomide has a therapeutic effect on neoplastic fever has yet to be elucidated. These intriguing features make the use of the drug potentially attractive for palliative care. In addition, by a distinct mechanism of action compared with most other drugs, thalidomide offers the possibility of combined treatment with other agents with non-overlapping toxicities.

The mechanism of action of thalidomide is probably based on the suppression of tumour necrosis factor- α and the modulation of interleukins. However, it is not possible to identify a single dominant mechanism, since the action of cytokines and the effect of thalidomide appear to be complex. This review article discusses the original uses and teratogenic effects of thalidomide within its historical context and, linking recent research at the molecular level with clinical findings, aims to provide the reader with insight into the current understanding of its biological actions, toxicities and potential benefits.

Thalidomide is known as one of the most infamous drugs of the twentieth century. When it was first introduced into the marketplace in the 1950s, the 'nonbarbiturate hypnotic'^[1] thalidomide was advocated to ensure a good night's sleep and to prevent morning sickness in pregnancy.^[2,3] However, soon after its approval in Europe in 1957,^[4] severe life-threatening birth defects observed in babies exposed to thalidomide *in utero* during early pregnancy were totally unexpected.^[2,3] In the long run, this apparently harmless drug turned out to be an

unmitigated disaster for the pharmaceutical industry and was responsible for more than 10 000 reported cases of birth defects.^[5]

In the pre-thalidomide era, testing regimens in various species in order to predict teratogenesis were not required.^[6] The teratogenic effect of thalidomide was later revealed to be species-specific in animal models, since it was difficult to elicit malformations in rat, mouse, hamster or chick embryos.^[6,7] In rabbits, however, fetuses from thalidomide-treated females were noted to have 'pronounced

abnormalities in long bone formation' resembling the thalidomide-induced embryopathy seen in the human fetus.^[6]

The use of thalidomide by pregnant women seeking relief from morning sickness led to an epidemic of fetal malformations such as phocomelia (short limbs), amelia (absence of limbs), hypoplasia or absence of the bones, external ear abnormalities, facial palsy, eye abnormalities and congenital heart defects.^[8] Abnormalities of the alimentary tract, urinary tract and other defects of internal organs have also been reported.^[8] This ultimately resulted in the withdrawal of thalidomide from the world market. A US marketing application was not approved after being reviewed in 1960 because of concerns about neuropathy associated with the use of the drug.^[4]

The thalidomide tragedy has led to significant changes in medical laws worldwide, resulting in requirements for demonstrated specific effectiveness of drugs and risks of adverse effects. Despite this tragedy, promising observations have resulted in the reintroduction of thalidomide into research and clinic.^[9] Indeed the US Food and Drug Administration (FDA) approved the use of thalidomide for the treatment of leprosy (Hansen's disease) in 1998. In response to the reappearance of thalidomide in the world market, a system has been developed to minimise any substantial risk of thalidomide-induced teratogenicity. Thalidomide is commercially available only through the System for Thalidomide Education and Prescribing Safety (STEPS) programme, a manufacturer-regulated system. To prescribe and dispense thalidomide, the healthcare provider must register with the STEPS programme. The prescriber and the patient are required to review and sign the consent form, which informs about contraception, frequency of pregnancy testing and other special requirements.^[5,8,10]

The purpose of this review is to discuss the pharmacology and potential clinical uses of thalidomide with particular emphasis on palliative care indications. Recent clinical research suggests further potential use of thalidomide as an adjunctive treatment in numerous serious medical conditions

including complications in infectious diseases, autoimmune and skin disorders, as well as several types of cancer and associated syndromes such as cancer cachexia. Thalidomide was shown to have a number of beneficial symptomatic effects on appetite, nausea, insomnia and pain. Some of these effects could be of significant value for patients in palliative care, as the teratogenic effects would not be a major concern in these patients.

1. Pharmacology and Utilisation

Thalidomide, α -(N-phthalimido)glutarimide, has the empirical formula $C_{13}H_{10}N_2O_4$ and a gram molecular weight of 258.2. The glutarimide moiety contains a single asymmetric centre and, thus, may exist in either of 2 optically active forms as S-(–) or R-(+). It has a net optical rotation of zero.^[8] The chemical structure of thalidomide is shown in figure 1.

1.1 Pharmacokinetics and Drug Metabolism

1.1.1 Absorption

The absolute bioavailability of thalidomide capsules in humans has not yet been well characterised, partly because of its poor aqueous solubility. The mean time to peak plasma concentrations (t_{max}) ranged from 2.9 to 5.7 hours in studies of both healthy volunteers and patients with leprosy, showing that it is slowly absorbed from the gastrointestinal tract.^[8] The observed peak concentration (C_{max}) increased in a less than proportional manner and the extent of absorption [as measured by area under the curve (AUC)] was proportional to dose in healthy volunteers.^[8] This lack of C_{max} dose proportionality, coupled with the observed increase in t_{max} values, suggests that the poor solubility of tha-

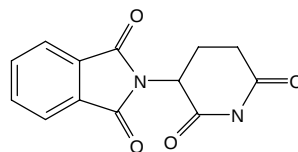


Fig. 1. Chemical structure of thalidomide.

lidomide in aqueous media may be limiting the rate of absorption.^[8]

When thalidomide was coadministered with a high fat meal, minor (<10%) changes in the AUC and $C_{\max}$ values occurred; however, $t_{\max}$ showed an increase to approximately 6 hours.^[8]

1.1.2 Distribution

The extent of plasma protein binding of thalidomide has not yet been determined. It is not known whether thalidomide is present in the ejaculate of males,^[8] but thalidomide and its metabolites were found in the rabbit semen ejaculates 'in appreciable amounts', detectable 'soon after oral ingestion of the drug, and for some considerable time afterwards'.^[11]

1.1.3 Metabolism

The exact metabolic route and fate of thalidomide in humans is not currently known. In theory, 'well over [a] hundred' possible metabolites may be found.^[12] The drug was reported to undergo non-enzymatic hydrolysis in plasma to various metabolites.^[12,13] In aqueous solutions at a pH of ≥ 6.0 , thalidomide has been found to rapidly form 3 primary products: 4-phthalimidoglutaramic acid, 2-phthalimidoglutaramic acid and α -(O-carboxybenzamido)glutarimide.^[14]

Although product information on thalidomide states that it does not seem to be hepatically metabolised to any large extent,^[8] co-incubation of the drug with human or rabbit liver microsomes yielded 5 primary metabolites of thalidomide: 4-OH-thalidomide, 3-OH-thalidomide, 3'-OH-thalidomide, 4'-OH-thalidomide and 5'-OH-thalidomide (see also section 1.3.3).

It has been suggested that thalidomide does not induce or inhibit its own metabolism, since it displayed similar pharmacokinetic profiles on the first and last day of administration in a repeat dose study in which 200 mg/day was administered to 10 healthy females for 18 days.^[8]

1.1.4 Elimination

Following a single dose, thalidomide has a mean half-life ($t_{1/2}$) of approximately 5 to 7 hours. As mentioned in section 1.1.3, the pharmacokinetics

of thalidomide are not altered with multiple administration. The renal elimination of thalidomide shows 0.7% excretion rate in the urine as unchanged drug while the renal clearance is 1.15 ml/min.^[8] Urinary concentrations of thalidomide were undetectable 48 hours after administration of a single dose. Even though thalidomide is thought to be hydrolysed to a number of metabolites,^[12-14] only 0.02% of the administered dose of 4-OH-thalidomide was detected in the urine of volunteers 12 to 24 hours after administration.^[8]

1.2 Pharmacokinetic Data in Special Populations

No significant differences in measured pharmacokinetic parameter values have been documented in HIV-seropositive individuals after a single dose administration of thalidomide (50mg capsule).^[8] Analysis of data from a small study of patients with leprosy suggests that thalidomide may have an increased bioavailability in these patients compared with healthy volunteers.^[8] Both an increase in $C_{\max}$ and an increased AUC have been observed in this population. The clinical significance of this increase has not been determined. Data from pharmacokinetic studies of healthy volunteers and patients with leprosy ranging in age from 20 to 69 years do not reveal any age-related changes, but there are no pharmacokinetic data available for individuals below the age of 18. Analysis of the data for thalidomide does not show any significant gender or racial differences in pharmacokinetic parameter values, but no trial specifically examining the effects of gender or race on thalidomide pharmacokinetics has yet been conducted.^[8] The pharmacokinetics of thalidomide in patients with renal dysfunction and hepatic disease has not been clarified.

1.3 Mechanism of Action

1.3.1 Cytokines

Thalidomide is an immunomodulatory agent with a spectrum of activity that is not fully understood.^[15] The use of thalidomide as an immunomodulator is currently being examined in conditions as diverse as erythema nodosum leprosum (ENL),

chronic graft-versus-host (GVH) disease (GVHD), gliomas, multiple myeloma, a variety of solid tumours, rheumatoid arthritis (RA), tuberculosis, sarcoidosis, aphthous ulcers, and HIV- and cancer-related wasting syndrome/cachexia. Current data suggest that the action of thalidomide may be related to several different mechanisms, including suppression of tumour necrosis factor (TNF)- α production, probably located at the transcription level,^[16-21] effects on interleukins (IL) and interferon (IFN)- γ ,^[18,20,22-27] down-regulation of selected cell surface adhesion molecules involved in leucocyte migration, and shifts in the ratio of CD4+ lymphocytes (helper T cells) to CD8+ lymphocytes (cytotoxic T cells).^[20,21,23-26] Cytokines are known to have numerous effects, and their interactions with thalidomide are complex and not all studies are consistent in their findings. Indeed, there are some studies that report contradictory observations. Overall, it does not seem possible to identify a single dominant mechanism of action for thalidomide. The multiplicity of actions may explain the large variety of therapeutic results achieved with the administration of thalidomide.

There are numerous reports indicating evidence for thalidomide-mediated suppression of production of TNF α .^[16-21] However, it has also been found to increase plasma TNF α levels in HIV-seropositive patients.^[28] It is possible that changes in the physicochemical conditions being studied *in vivo* or *in vitro* may affect the relationship between thalidomide and TNF α . Although thalidomide spontaneously hydrolyses at pH 7.4 to various metabolites,^[13,14] a recent study demonstrated that it increases IL-2 and suppresses TNF α levels *in vitro* only as an intact molecule.^[13] In addition, thalidomide was observed to be metabolised species-specifically by liver microsomes.^[14] These findings underline the need to investigate the complex action of thalidomide under appropriate physicochemical conditions.

Further insight into the effects of thalidomide on TNF α can be gained by comparing its effects with those of other drugs with putative effects on TNF α , pentoxifylline and dexamethasone. De-

spite evidence of TNF inhibition by both thalidomide^[16-21] and pentoxifylline,^[29] only thalidomide was 'capable of improving the subjective symptoms of cachexia in advanced cancer patients' in one study.^[30] Another study demonstrated only a 50% reduction of TNF production capacity during the treatment of RA with pentoxifylline and thalidomide as adjuvants.^[19] The levels of IL-6, IL-10 and IL-12 remained unaffected. It has not been determined how pentoxifylline might interact with the action of thalidomide *in vivo*, but the authors of the study believe that the coadministration of pentoxifylline and thalidomide 'is rather toxic' because of the multiple adverse effects observed.

Corticosteroids such as dexamethasone are thought to inhibit a variety of cytokines (IL-2, IL-4, IL-6, IL-10, IL-12, IFN γ and TNF α) in a dose-dependent manner. The thalidomide-induced inhibition of IL-12 production appeared to be additive to that caused by dexamethasone in a study by Moller et al.,^[22] who found that this mechanism was independent of known endogenous inhibitors of IL-12 production. Supporting the theory of a unique mechanism of action, a further study shows that thalidomide appears to selectively suppress IL-6 and TNF α in human blood mononuclear cells *in vitro*.^[18] The levels of IL-2, IL-4 and IL-10 remained unaffected by thalidomide in contrast to dexamethasone, which markedly inhibited the expression of all cytokines. The authors conclude that thalidomide and dexamethasone, although they both act at the level of transcription, influence separate pathways because of their significantly different effects on cytokine production. Furthermore, corticosteroids resemble thalidomide with their known anti-emetic properties,^[31] and ability to improve asthenia^[31] and pain control.^[31,32] The observation that thalidomide acts additively and synergistically with these therapeutic actions of corticosteroids^[18,22] offers the possibility of its use in a steroid-sparing approach.

There is variability in the reported relationship between thalidomide and cytokines such as IL-2, IL-6, IL-12 and IFN γ . Several studies have reported thalidomide-mediated increases in IL-2^[33,34]

and IL-2-related phenomena, such as increased IL-2-mediated T cell proliferation^[23] as well as elevated production of soluble IL-2 receptors.^[27] However, there are also investigators who found no association between thalidomide and IL-2.^[35,36] Inconsistencies have also been found in the impact of thalidomide on IL-6. Two studies mention a reduction of IL-6 level due to the influence of thalidomide,^[18,20] whereas in 2 others IL-6 level was unaltered.^[16,19] The level of IFN γ was found to be elevated,^[23,24,27] decreased^[18] or not altered at all by thalidomide.^[20] Finally, the production of IL-12, a cytokine known to be critical in the pathogenesis of the cellular immune response in ENL, chronic GVHD, sarcoidosis and RA, was shown to be potently suppressed by thalidomide in human peripheral blood mononuclear cells.^[22] The effect was concentration-dependent. However, other studies did not observe any effect of thalidomide on the level of IL-12.^[19,20]

1.3.2 Cellular Immunity

Mast cells, neutrophils and TNF α are closely related in the pathogenesis of inflammatory reactions.^[37,38] Neutrophils, a homogenous population of effector cells, are known to be rapidly attracted in large numbers to sites of inflammation in order to form an early response to infection or injury. *In vitro* administration of thalidomide was shown to inhibit neutrophil chemotaxis, whereas it modulated TNF- and IL-1-induced chemotaxis in a 'bimodal manner'.^[39] Thalidomide also led to a decreased dermal infiltration of neutrophils and T cells besides a reduction of TNF α levels in patients with systemic ENL.^[21]

1.3.3 Angiogenesis

Orally administered thalidomide has been demonstrated to inhibit angiogenesis induced by basic fibroblast growth factor (bFGF) in the rabbit cornea micropocket assay.^[40] The authors hypothesise that the ability of thalidomide to inhibit angiogenesis induced by pharmacological doses of bFGF might result from a direct inhibition of an essential component of angiogenesis, independent of its effects on TNF α production. In another report, thalidomide also inhibited corneal angiogenesis in the

rabbit induced by vascular endothelial growth factor (VEGF).^[41] However, a subsequent study showed that thalidomide failed to inhibit tumour growth and angiogenesis *in vivo* in solid tumours in mice.^[42] Mice in both the control group and the group receiving orally administered thalidomide developed an intact network of new blood vessels.

It has been concluded that the anti-angiogenic effects of thalidomide only occur after species-specific metabolic activation of the drug, similar to the teratogenesis associated with the use of the drug.^[14] Using a rat aorta and human aortic endothelial cell models, an inhibition of angiogenesis by thalidomide was only observed when the drug had been co-incubated with human and rabbit liver microsomes, not in the presence of rat liver microsomes.^[14] These studies^[14,40,41] imply that thalidomide only seems to have an effect on growing vessels when given systemically.

2. The 'Early View' of Thalidomide

When thalidomide was introduced to the German market in 1956, and to the UK and other countries after 1958,^[5] it was discovered to be an effective hypnotic^[43,44] and was prescribed as a sedative and anti-emetic, in particular during pregnancy.^[2,3,45] The early original uses of thalidomide are summarised in table I. Thalidomide seemed to be advantageous for the treatment of insomnia (50 to 200mg) and as a 'nonbarbiturate hypnotic', since it appeared to lack the dependence and hangover effect produced by barbiturates.^[44] Thalidomide was also administered as a 'sedative in mildly restless, irritable and anxious patients (50 to 75mg daily)'.^[43] A British publication^[44] explained the need for sedatives such as thalidomide in the el-

Table I. Original uses of thalidomide

Classification	Use
'Nonbarbiturate hypnotic'	Insomnia
Sedative	Anxiousness, restlessness in the elderly
Anti-emetic	Morning sickness, hyperemesis gravidaris
Adjuvant analgesic	Pain

derly as follows: 'To select a suitable sedative and hypnotic for the restless, noisy or confused elderly patient is a commonly recurring problem in geriatric practice. In many cases the main reason for admission to a geriatric unit is the inability to achieve satisfactory sedation in the home'. In this comparative clinical trial thalidomide was recognised as superior to other existing drugs for nonbarbiturate alternatives in the management of insomnia. The apparent safety of thalidomide, its prompt action and the fact that no lethal dose could be established in animal studies, made it rapidly popular and the drug obviously met a high demand for such a sedative.

During the early thalidomide era, thalidomide was found to increase the analgesic efficacy of 'APC' [aspirin (acetylsalicylic acid) 450mg, phenacetin 325mg, caffeine 65mg] by testing 'normal volunteers, using electrical stimulation of teeth'.^[46] By comparing APC versus thalidomide 25mg plus APC versus codeine 32mg plus APC, but not versus thalidomide or codeine alone, it was found that 'with each of the mixtures the rise in threshold was greater and the rise persisted longer (120 minutes instead of 40 minutes with thalidomide and 140 minutes instead of 60 minutes with codeine) than with APC alone'. Thus, based on these observations thalidomide has been explored as a potential adjunct analgesic.

McBride^[2] and Lenz^[3] were the first to document an association between maternal thalidomide use and the sudden high incidence of limb and internal malformations of their infants, which led to the withdrawal of thalidomide from the world market in 1961.^[2,3] It has been estimated that 10 000 to 12 000 infants were affected by thalidomide-induced birth defects.^[5]

3. Clinical Effects and Applications

3.1 Central Nervous System Effects

Because of its mild hypnotic, anxiolytic and anti-emetic effects it is obvious that thalidomide has significant central nervous system effects. However, these effects are poorly understood. Thalidomide

has been demonstrated in brain tissue of both rats^[12] and humans,^[47] and findings in 1966 suggest it can possibly induce gross anatomical changes in the brain.^[48] To what extent and via which mechanism thalidomide may affect the brain tissue has to be further determined.

3.2 Peripheral Nervous System Effects

Although thalidomide is capable of inducing neuropathy as a serious adverse effect,^[24,28,49,50] it has also been shown to alleviate neuritis associated with leprosy.^[50] Neuropathy, following administration of thalidomide, represents the most common serious adverse effect of thalidomide. Experimental autoimmune neuritis (EAN) is a CD4+ T cell-mediated demyelinating autoimmune disease and is considered as an animal model for the study of the immunopathogenesis and immunotherapy of Guillain-Barre syndrome.^[24] In rats, EAN was prolonged by thalidomide, which was thought to be consistent with the clinical polyneuropathy reported in patients receiving treatment with thalidomide.^[24] The suppression of IL-6^[18,20] by thalidomide might explain the finding of neuropathy in patients with long term and high dose administration of thalidomide, because IL-6 appears to contribute to the survival of axotomised neurons.^[51]

3.3 Antineoplastic Use

The use of thalidomide as an anti-angiogenic agent is currently being discussed for gliomas, metastatic melanoma, renal cell, ovarian, prostate and breast cancer, Kaposi's sarcoma and multiple myeloma.^[52-55]

By 1965, a study of 21 patients with advanced malignancy had already examined a possible anti-angiogenic effect of thalidomide but could not show objective regression of the disease.^[56] However, a 'significant subjective palliation' in 7 patients was documented, which the authors related to an improved sedation.

In a Lewis Lung tumour model, thalidomide administration reduced the radiosensitivity of the tumour, but increased 'its sensitivity to combined treatment with radiation and the bioreductive cyto-

toxin tirapazamine' and additionally reduced the incidence of lung metastases from primary Lewis Lung tumours.^[57] The authors hypothesise that these findings may be based on an elevated tumour hypoxia, possibly due to an anti-angiogenic mechanism, and may present a new perspective for combined therapy. Agents that have both immunomodulatory and anti-angiogenesis properties, such as thalidomide, may also show advantages when combined with chemotherapy.

Tumour growth delay was found to strongly correlate with tumour blood flow reduction and to be related to tumour TNF levels, but not to serum-induced TNF levels.^[58] Although thalidomide reduced the serum TNF response to an anti-tumour agent known to induce the synthesis of TNF α , it unexpectedly potentiated its anti-tumour effect. These findings represent another example of the diversity of action observed with the use of thalidomide and could be considered for future studies.

Thalidomide has been shown to have anti-angiogenic properties in preclinical studies.^[14,40,41,57,58] Although some studies failed to demonstrate a sufficient anti-cancer efficacy,^[42,56,59,60] others could show that the anti-angiogenic potential of thalidomide may have important implications for tumour growth with metastatic spread.^[40,41,52,53,57] Early^[49,50,56] and recent clinical trials have reported that thalidomide appears to be a well tolerated anti-angiogenic agent that is biologically active in some tumours.^[52-54,61,62] In a phase II study the anti-angiogenic treatment of metastatic melanoma, renal cell, ovarian and breast cancers was documented, and the response to treatment was not reflected by the changes in serum and urinary VEGF.^[53] The patients received thalidomide 100mg until progression. Three patients showed 'differential response', 10 patients had stable disease for 8 to 25 weeks (median 12 weeks) and 8 patients still continued on treatment at that point in time. Quality-of-life data analysis suggested an improvement in appetite and sleeping. Only mild neurotoxicity was detected. Finally, a recently published series of patients with refractory myeloma showed that thalidomide 200 to 800 mg/day can induce marked and durable re-

sponses in some patients, including patients previously treated with high dose chemotherapy.^[55]

3.4 Leprosy, Erythema Nodosum Leprosum

In 1998, the FDA approved thalidomide for the treatment of ENL. A chance observation in the 1960s^[4,50] led to the conclusion that thalidomide might be useful in the treatment of patients with ENL, an inflammatory reaction associated with leprosy. Subsequently, many controlled and uncontrolled trials were published reporting effectiveness of the drug in controlling the cutaneous manifestations of ENL, and the World Health Organization recommended the drug as being effective in treating this disorder.^[49] Under an investigational new drug application, thalidomide was used in the US for the treatment of ENL for 20 years overseen by the US Public Health Service.^[4] Thalidomide was shown to be effective in ENL,^[49,50,63,64] even to possess anti-pyretic properties,^[49,64] and offers the possibility of a steroid-sparing treatment.^[49,63,64]

The morbidity of active ENL is characterised by general toxicity and/or acute inflammation in affected tissues, such as nerves and joints, and typical painful subcutaneous nodules. Thalidomide treatment in ENL has been observed to provide better symptomatic control and to cause fewer adverse effects than corticosteroids.^[5] A significant reduction of corticosteroid requirement (61 to 100%) could be achieved when thalidomide was combined with corticosteroids in a double-blind controlled trial of patients with severe chronic ENL.^[63]

Woodcock,^[4] in a review of two double-blind controlled trials,^[49,50] is convinced of the beneficial effect of a short course treatment of thalidomide on fever and skin lesions in acute ENL. Besides eliciting a 92% response rate, thalidomide was actually found to be more effective than aspirin at reducing fever in ENL.^[49] Further evidence for the anti-pyretic properties and efficacy of thalidomide in the symptomatic control of ENL is provided from the controlled study of 43 patients published in 1966 by Opromolla et al.^[64] TNF α , IL-1 and IL-6 are three inflammatory cytokines that independently activate the hypothalamic-pituitary-adrenal axis and

act synergistically when used in combination.^[65] The effectiveness of thalidomide in ENL is probably attributable to its inhibition of $\text{TNF}\alpha$,^[21] with subsequent amelioration of inflammation. An example of this is provided in the observation of a reduction of dermal infiltration of neutrophils and T cells, as well as a down-regulation of intercellular adhesion molecule and major histocompatibility complex class II antigens due to thalidomide.^[21]

In addition to its effects on cellular immune mechanisms, thalidomide has also been shown to have impact on humoral immunity. It significantly inhibits immunoglobulin (Ig)M antibody formation in mice when immunised with sheep erythrocytes, and has been observed to selectively decrease serum IgM levels in patients with leprosy receiving thalidomide.^[66] Shannon and colleagues^[66] have associated the pathogenesis of ENL with the Arthus-type hypersensitivity reaction and, therefore, they see a possible explanation for the mechanism of thalidomide in ENL, since complexes of antigen and antibody would contribute to the clinical manifestation of vasculitis and painful subcutaneous nodules. An explanation for the anti-inflammatory and possibly secondary analgesic mechanism of thalidomide in ENL could be that it simply suppresses this phenomenon.

3.5 Aphthous Ulcers in HIV Infection and Behcet's Disease

Thalidomide appears to be highly effective in mucocutaneous diseases such as aphthous ulcers that occur frequently both in patients with HIV infection and those with Behcet's disease.

In a series of 12 patients who have HIV infection and pharyngeal hyperalgesia (9 with confirmed AIDS), thalidomide was found to be capable of healing the ulcerated lesions and completely suppressed the pain.^[67] Moreover, in a double-blind, randomised, placebo-controlled study 24 of patients with HIV infection and oral aphthous ulcers, the pain was reduced and the ability to eat was improved with thalidomide treatment.^[28] However, increased HIV RNA levels and an unexpected increase in the plasma levels of $\text{TNF}\alpha$ and soluble

$\text{TNF}\alpha$ receptors were also found in this study - findings which are in conflict with the expectations based on the theory that thalidomide inhibits $\text{TNF}\alpha$.

Based on a reported healing rate of approximately 80% in anecdotal individual case reports, thalidomide is thought to be useful in Behcet's disease and complex aphthosis, and might represent a good maintenance therapy.^[5] Thalidomide, at a dosage of 100 mg/day, was observed to be sufficient to heal the majority of new lesions within 1 week. A further study consistently recommended the daily dose of 100mg, and found thalidomide to be an advantageous drug in treating 'necrotic aphthae, mutilating and recurring mucocutaneous aphthosis' and 'also being useful in controlling some symptoms of Behcet's disease'.^[68] A non-blind study conducted by Genvo et al.^[69] in 1984 found that the treatment of aphthosis with both thalidomide 200 to 300 mg/day alone and in combination with colchicine 2 to 3 mg/day to be effective, and documented a 'rapid healing of mucous lesions and a rapid reduction of pain and burning'. The maintenance dosage of 50 to 100 mg/day was effective.

3.6 Tuberculosis, Sarcoidosis, HIV Infection

The pro-inflammatory cytokines $\text{TNF}\alpha$, IL-1 and IL-6 appear to play an important role in the pathogenesis of the cachexia/anorexia syndrome. In a mouse model of experimental murine tuberculosis, thalidomide treatment significantly reduced the levels of $\text{TNF}\alpha$, IL-6 and IL-10 protein in the blood and mRNA expression in the lungs.^[20] However, IL-12 and $\text{IFN}\gamma$ were not altered by thalidomide. The lung pathology showed smaller granulomata with apoptotic cells but no necrosis, while the bacillary load was not altered by thalidomide.

Patients with HIV and patients with both HIV-1- and tuberculosis-associated bodyweight loss consistently experienced bodyweight gain following administration of thalidomide.^[27,70] In patients with HIV infection, thalidomide treatment alone led to bodyweight gain, related to a reduction in daily urinary nitrogen excretion and lean tissue

anabolism, even when a constant caloric intake had been documented.^[27]

3.7 Graft-versus-Host Disease

By 1966 thalidomide had already been shown to suppress GVH reactions in both the chick embryo and the rat, each receiving injections of lymphoid cells from a donor of their own species.^[71] The extent of induced splenomegaly, considered as being directly related to a generalised GVHD reaction, was measured and the degree of reduction in thalidomide-treated animals interpreted as inhibition of GVHD. Thalidomide was shown to significantly reduce the severity of the GVHD but not to suppress it completely.

Chronic GVHD is known to be the most common late complication of allogeneic bone marrow transplantation, and some clinical trials show thalidomide to be effective in GVHD. In a study examining children with refractory chronic GVHD secondary to allogeneic bone marrow transplantation, 6 of 14 children showed complete response to thalidomide in a median time of 2 months.^[72] In a presentation of a preliminary study of patients with either higher risk or refractory chronic GVHD, 14 patients had a complete response, 12 patients had a partial response and no response could be observed in 18 patients who showed a 59% response rate to treatment with thalidomide.^[73] However, although some studies suggested a beneficial effect, others provided less support for the use of thalidomide in chronic GVHD.^[5] In the prophylactic setting, Chao et al.^[74] reported that patients receiving thalidomide 200mg twice daily beginning 80 days after bone marrow transplant, developed chronic GVHD more often than patients receiving placebo. Moreover, an apparent overall survival advantage was noted for patients receiving placebo compared with those receiving thalidomide.^[74] This latter study indicates that the timing of thalidomide administration in the bone marrow transplant setting may be important.

3.8 Rheumatoid Arthritis

TNF α has been suggested to play a key role in the pathogenesis of RA, and thus there has been speculation that treatment with thalidomide might lead to clinical improvement in patients with active RA. In a nonblind study of 7 female patients with RA, oral administration of thalidomide (6.9 to 15 mg/kg/day) resulted in 'clinical improvement within several weeks' and significantly decreased the rheumatoid factor titre in 'several' patients.^[75] In another nonblind study of 17 patients receiving thalidomide for the treatment of severe or refractory RA, 7 experienced complete remission, 5 partial remission, 3 showed no improvement and 2 withdrew.^[62] The authors see a justification for further controlled trials. However, only limited efficacy was noted in a nonblind study of 12 patients in the treatment of RA combining pentoxifylline and thalidomide.^[19]

3.9 Other Conditions

The use of thalidomide has also been discussed for therapeutic use in pyoderma gangrenosum, inflammatory bowel disease, Sjögren's syndrome and discoid lupus erythematosus,^[5] but further controlled trials are necessary to better assess its role. One such trial was recently conducted in patients with toxic epidermal necrolysis. In the group of patients receiving thalidomide there was no statistically significant elevation of TNF α levels, but the study was stopped prematurely (after 10 patients per study arm) because of an excess mortality in the thalidomide group.^[76] A summary of the novel uses of thalidomide in specific conditions is shown in table II.

3.10 Uses in Palliative Care

Thalidomide was originally found to be a new advance in the symptomatic relief of insomnia and nausea. In addition to these still remaining indications, its immunomodulatory, antipyretic, anticachectic, possible anti-angiogenic and potential analgesic effects offer a broad spectrum of action that is well matched with the therapeutic needs of pal-

Table II. Novel uses of thalidomide in specific conditions

Leprosy (Hansen's disease)
Chronic illness syndromes, e.g. cachexia
Tuberculosis, sarcoidosis
Aphthous ulcers in HIV syndrome and Behcet's disease
Graft-versus-host disease
Pyoderma gangrenosum
Inflammatory bowel disease
Rheumatoid arthritis
Sjögren's syndrome
Discoid lupus erthematosus
Multiple myeloma
Advanced solid tumors, e.g. renal cell carcinoma

liative care medicine. A list of the potential palliative care applications of thalidomide is shown in table III.

Research conducted in the early era of thalidomide did not follow currently recommended methodologies for clinical trials. In addition, central drugs used for their potential role as an anti-emetic, analgesic or hypnotic were not available for these symptoms then. Therefore, the potential role of thalidomide in this field needs to be re-established in placebo-controlled and comparative clinical trials.

3.10.1 Insomnia

Insomnia is a frequent problem in patients with advanced cancer and terminal diseases.^[77] Benzodiazepines are generally poorly tolerated in these patients because of their borderline cognitive function and the multiple medications they are receiving, including opioids and psychotropics.^[78] The effect of thalidomide on certain sleep spindles (manifestations of sleep on electroencephalograms) has not yet been examined. Early studies recognised that thalidomide was effective as a mild hypnotic and anxiolytic in the elderly, and reported an absence of hangover, which would be useful in this debilitated population.^[44] The somnolence seen in a recent phase I trial of thalidomide (4 dosage levels: 200, 300, 400, 600 mg/day) in patients with AIDS-related Kaposi's sarcoma was dose-dependent.^[79] With the highest dosage of thalidomide (600 mg/day), two-thirds of patients discontinued the medication.

To maintain the highest possible quality of life, cognitive and psychomotor function should be maintained in patients requiring palliative care. In the short term management of insomnia, thalidomide should be compared with short- and medium-acting benzodiazepines and the newer nonbenzodiazepine hypnotics. Additionally, the interaction with opioid analgesics should be studied.

3.10.2 Cachexia and Chronic Nausea of Cancer

Cachexia is known to occur in most patients with advanced cancer. Its prevalence in the literature seems to vary between 31 and 87%, with most studies reporting a frequency higher than 50%.^[80] Patients with this wasting syndrome experience diverse symptoms such as progressive bodyweight loss, chronic nausea, fatigue, sleep disorders and complain of a decreased sensation of well-being. In recent years, cancer cachexia has been understood to result from major metabolic disarray because of complex mechanisms involving tumour by-products and host cytokine release, in particular TNF α , rather than a simple increase in energy consumption by the tumour and starvation by the patient.^[80-87] Thalidomide is capable of significantly influencing cytokine levels and may play a pivotal role in the therapeutic immunomodulation of patients with advanced cancer.

Cytokines, such as TNF, IL-1, IL-6 and IL-8, have been shown to induce anorexia/cachexia by lipolysis and other metabolic effects, as well as by direct action in the CNS.^[81-87] IL-6 has been demonstrated to be a key mediator of fever and food intake in an experimental sepsis model of 'knock-out' mice.^[85] The lack of IL-6 did not affect lethality in response to sepsis, but production of TNF

Table III. Potential uses of thalidomide in palliative care

Cancer cachexia/anorexia
Chronic nausea
Insomnia
Neoplastic fever
Profuse sweating
Angiogenesis
Pain

was responsible for lethality and initial hypothermia in these mice.

The administration of thalidomide in 37 evaluable patients with advanced cancer with cachexia led to significant improvement in appetite, nausea and sensation of well-being in a preliminary study published by Bruera et al.^[61] Thalidomide has also been successfully used in halting and reversing bodyweight loss in AIDS-associated cachexia, which is similar to cancer cachexia with high levels of TNF α .^[27,28,70] Moreover, in a randomised, double-blind study, patients with simultaneous HIV-1 and tuberculosis infection showed a higher mean bodyweight gain during treatment with thalidomide than a group of patients with HIV-1 infection only.^[70] In summary, these results suggest a beneficial effect of thalidomide in the therapy of cachexia in chronic illness, probably via a mechanism suppressing TNF α .

Chronic nausea is a distressing and frequent symptom in patients with cancer and terminal diseases, and its causes are multiple, including opioid-induced constipation, autonomic failure and metabolic abnormalities.^[87] The prevalence of chronic nausea reported in the literature varies from 21 to 68%.^[87] In the early era of thalidomide, the drug was used as an anti-emetic in hyperemesis gravidarum,^[2,45] and was found to be effective in the symptomatic therapy of nausea and vomiting caused by malignant nongastric neoplasms or by the administration of chlormethine.^[88] Recently thalidomide has been shown to be particularly effective in improving appetite and overall sensation of well-being in patients with cachexia due to terminal cancer.^[61]

These findings suggest a potential role of thalidomide in cachexia and chronic nausea of cancer. Because of the different adverse effect spectrum and likely mechanism of action, thalidomide could be coadministered in prospective studies with established, but not very effective drugs for cancer cachexia including megestrol,^[89] fish oil^[90] or adrenergic anabolic drugs such as clenbuterol,^[91] in order to achieve a synergistic effect. Future studies should attempt to further characterise the clinical effects of thalidomide, including its effect on body-

weight and other nutritional variables such as caloric intake and body composition.^[92]

3.10.3 Neoplastic Fever and Profuse Sweating

Both fever and sweating are frequent and distressing complications in terminally ill patients with cancer. The marked effects of thalidomide on fever associated with ENL^[49,64] suggest that thalidomide might be useful in some patients with neoplastic fever. The mechanism of neoplastic fever is thought to involve inflammatory cytokines such as TNF α , IL-1 and IL-6 that are produced either by host macrophages in response to the tumour or by the tumour itself.^[61,85,86,93,94] However, at present there are no reports of the use of thalidomide in neoplastic fever.

Since thalidomide has been shown to modulate TNF α - and IL-1-induced chemotaxis,^[39] as well as to suppress IL-6^[18,20] and TNF α ,^[16,18-21] the antipyretic effect of thalidomide might simply be explained by the suppression or modulation of these inflammatory mediators.

A reduction of sweating has been documented as an adverse effect associated with thalidomide-induced neuropathy.^[95] Furthermore, there have been observations that thalidomide may play a role in reducing the distress of sweating in terminal malignancy. Two letters^[96,97] describe a long-lasting resolution of profuse night sweats in patients with advanced malignant disease following oral administration of thalidomide 100mg.

The antipyretic and antidiaphoretic effects should be tested in studies comparing thalidomide with standard drugs of limited efficacy such as paracetamol (acetaminophen) or nonsteroidal anti-inflammatory drugs. The effects on sweating are of special interest because of the highly distressing nature of this symptom and the lack of effective drugs for its management.

3.10.4 Pain

60 to 90% of patients with advanced cancer have been reported to experience substantial pain.^[98] Neuropathic pain occurs frequently in patients with terminal cancer, mainly as a result of involvement of the spinal cord, nerve roots or peripheral nerves.^[99] Since pain is one of the most disturbing symptoms,

it emphasises the importance of adequate pain management in terminally ill patients.

Cytokines such as TNF and the interleukins can potentially modify nociception and synaptic transmission, and are thought to be involved in the cascade of actions resulting in neuropathic pain.^[51,100-105] Pain perception may therefore be therapeutically influenced by modulation of cytokines.

Thalidomide was originally known to have adjuvant analgesic effects,^[46] and was discovered early on to be effective in the control of the painful subcutaneous nodules in leprosy patients in whom TNF levels are elevated.^[21,49,50] In recent years it has been shown to be effective for the therapy of oral mucocutaneous ulcers/apthosis found in HIV/AIDS syndrome and Behcet's disease by completely suppressing or rapidly reducing sensations of 'pain and burning'.^[28,67-69]

In a rat model of neuropathic pain (chronic constriction injury model), pre-emptive treatment with thalidomide reduced mechanical allodynia and thermal hyperalgesia during the early stage of the disease.^[102] Both TNF α immunoreactivity in the endoneurium and pathological vascular changes were found to be reduced after treatment with thalidomide. The course of pain-related behaviour could not be altered by starting treatment with thalidomide when hyperalgesia was already present. It has been suggested that TNF α is involved in the pathogenic mechanisms of neuropathic pain by affecting endothelial cells and up-regulation of receptor sensitivity in afferent nerve fibres.^[104]

TNF α and IL-6 appear to play a key role in pain mechanisms. TNF α has been shown to be present in the granules of resident mast cells and seems to mediate mast cell-induced initiation of some inflammatory reactions.^[37,38] Considered to be a signalling molecule of injured nerves, TNF α is thought to induce stimulation of IL-6 synthesis in many cell types, including cortical neurons *in vitro*.^[39,103]

IL-6 is virtually absent in the peripheral nervous system of normal mature animals and can only be detected in the nerve for approximately one day following transection.^[104] IL-6 induces allodynia and hyperalgesia via actions in the dorsal horn of

the spinal cord,^[103] and modifies sensory responses in the cortex as well as eliciting nociception upon intracerebroventricular administration to rats via a mechanism involving prostaglandins.^[105] It has also been demonstrated that IL-6 synthesis, induced by an injury factor arising from the nerve stump in a rat model, contributes to the mechanism of pain as well as to the survival of injured peripheral neurons.^[48]

In summary, the analgesic properties of thalidomide might be based on its selective suppression of immune-mediators such as IL-6 and TNF α . This mechanism may provide one explanation for the analgesic effect of thalidomide in several conditions such as ENL, aphthous ulcers and inflammatory syndromes. Since the drug has been found in brain tissue,^[12,47] a further potential mechanism of action of thalidomide as an analgesic could be a direct effect on the brain, as it occurs with its hypnotic and anti-emetic effects.

In the patient requiring palliative care, the analgesic properties of thalidomide on neuropathic pain might be particularly useful for severe cancer-induced plexopathies. This would be especially beneficial given the refractory nature of neuropathic cancer pain.^[98,99] However, in such a situation, the patient should be monitored carefully regarding the possibility of thalidomide-induced neuropathy.

4. Adverse Effects

Essentially, the risks related to thalidomide remain the same today as when the product was originally marketed in more than 45 countries approximately 40 years ago. Since various patient populations have been exposed for decades of clinical use, the overall adverse reaction profile of thalidomide is well understood. The adverse effects in patients over the age of 65 years do not appear to be different in kind from those reported for younger individuals.^[8] The more frequent or severe adverse events are outlined below and summarised in table IV.

4.1 Teratogenesis

As mentioned in the introduction, one reason that thalidomide failed in animal models to have

Table IV. Adverse effects of thalidomide

Teratogenesis
Neuropathy
CNS effects, e.g. drowsiness
Allergic drug reactions
Haematological effects
Increased viral load in HIV-infected individuals
Drug interactions

the teratogenic effects observed in humans was its species-dependent action.^[6,7] Various animal models have subsequently been explored in order to further characterise the different actions of thalidomide.

4.1.1 Thalidomide in Animal Models

Producing malformations in rats, mice, hamster or chick embryos seemed to be a 'difficulty', whereas teratogenesis was more easily inducible in the rabbit.^[6,7]

In 1965 it was postulated that thalidomide rapidly crosses the placental barrier of rabbits because of its lipid-soluble characteristics.^[7] However, in the rabbit fetus, thalidomide was found to be hydrolysed non-enzymatically to polar compounds ($t_{1/2}$ about 2.5 hours) which traverse the placental barrier slowly and therefore accumulate in the fetus. 24 hours after administration of radioactive-labelled thalidomide to a pregnant rabbit, the plasma concentration of thalidomide in the fetus was increased approximately 20-fold compared with the maternal plasma concentration.

In the 1960s, two main opinions prevailed on the mechanism of thalidomide-induced teratogenesis. One group considered the action of thalidomide to result from its effect as an antagonist of vitamins of the A and B group,^[106-108] whereas the other group hypothesised the drug was an antagonist of glutamic acid/glutamin metabolism.^[109,110] Conclusions leading to this antagonist theory were often not based on scientific experimental evidence, but were rather drawn from structural similarities noted between certain compounds and thalidomide. More recently, neither mechanism has received much attention. A third possibility considered at that time, namely of

a structural resemblance between thalidomide and nucleosides,^[111] also obviously failed to bear fruit.

4.1.2 Thalidomide in Humans

McBride^[2] and Lenz^[3] were the first to correlate the high incidence of malformations with the administration of thalidomide to pregnant women. A high susceptibility of the fetus for thalidomide-induced malformations has been found between the thirty-fourth and fiftieth day postmenstruation.^[2,45,56,112] It has been documented that thalidomide may cause malformations even after a single dose of a 50mg capsule by a pregnant woman.^[8]

Most of the thalidomide-induced abnormalities reported affected both limbs and internal organs, resulting in phocomelia (short limbs), amelia (absence of limbs), hypoplasticity or absence of the bones, external ear abnormalities, facial palsy, eye abnormalities and congenital heart defects, malformations of the alimentary tract, urinary tract and other defects.^[112-115] A 'so far almost unobserved agenesis of the appendix'^[112] was documented as well as the fact that in 25% of thalidomide malformed babies 'the typical lesion described is a coloboma of the iris and choroid'.^[115]

Thalidomide was detected in the brain tissue of cadavers from patients who had received thalidomide.^[47] Although it has been reported that 'thalidomide attacks the skeleton, the heart, the intestines, the kidneys and the ears', the brain was 'usually spared',^[113] and thalidomide-affected children were found to be 'mostly well developed mentally'^[113] and to have 'at least average intelligence and should benefit from normal education'.^[115] A report of twins with both limb and internal organ malformations, consistently documented normal brain anatomy.^[113]

However, in 1966, pathological findings documented abnormalities in brain gross anatomy in addition to electroencephalographic and neurological deviations.^[48] Nonetheless, the author emphasises that in most thalidomide-malformed children with abnormalities of internal organs and limb defects an 'intact cerebrum can be expected', and that no psychological or intellectual differences can be observed compared with healthy children.

4.2 Mutagenesis

The issue of whether or not thalidomide is mutagenic has been explored since the 1960s. At that time several studies examined the karyotypes of children with thalidomide syndrome and showed various results. Hirsch^[116] studied 5 children diagnosed with thalidomide embryopathy and determined their chromosomal status. The evaluation of a total of 275 metaphase plates revealed a significant increase in aneuploid cells (35.2 versus the normal of 10%; mainly hypoploid). No structural anomalies were observed.^[116] Another study^[117] found a variation of the mitotic action in the metaphases of leucocytes of thalidomide-affected children and concluded that thalidomide 'affects not only limb formation but also the immunological properties of the leucocyte surface'. Moreover, an *in vitro* study^[118] revealed the occurrence of aberrations such as chromatid and isochromatid gaps, breaks with formation of small acentric fragments as well as a few deletions and translocations when thalidomide was added to the human lymphocyte culture from 3 healthy donors.

More recently, 2 papers dispute the possibility that thalidomide might cause second-generation defects. Both emphasise that the hypothesis that thalidomide might be a mutagen lacks a scientific foundation. The authors conclude that children of individuals affected by the teratogen thalidomide are unlikely to inherit similar abnormalities.^[119,120] Clearly, the issue of mutagenesis related to thalidomide remains controversial. Nevertheless, because of its teratogenic and possible mutagenic potential, any influence of thalidomide on the fetus has to be avoided. Thalidomide should not be used in female patients who are or could become pregnant, or in male patients who could engage in sexual relations that could result in pregnancy. While this is a major limitation in the younger patient population, it has minimal relevance in palliative care of patients with advanced cancer.

4.3 Effects on the Nervous System

4.3.1 Acute Effects

Thalidomide seems to have marked CNS effects, since it has known sedative properties, and thus drowsiness and somnolence may be expected events in a proportion of patients receiving this drug. Thalidomide may therefore be useful for patients who have insomnia. In situations where the sedative effect is not desired, it can be mitigated or avoided by administration at bedtime, since early papers state that thalidomide at low dose lacks a hangover effect.^[44] Possibly associated and fairly frequent effects include tremor, lowered blood pressure and pulse rate, bradycardia, dizziness and orthostatic hypotension.^[4,6,8,21,43,49]

As thalidomide obviously affects the CNS, and since drowsiness/somnolence, 'twitching of the limbs^[43]' and constipation^[19,43,49,50,52,62,75] have been associated with its use, it has to be determined under which conditions thalidomide might potentially cause similar adverse effects as cannabinoids and opioids or may interact with these drugs when combined.

4.3.2 Neuropathy

Peripheral sensory neuropathy is a known complication of thalidomide therapy^[6,49,95] and presents probably the most significant risk to patients receiving the drug. Paraesthesias including numbness and tingling sensations, hyperaesthesia for pain and temperature, especially in the hands and feet, as well as disturbances of autonomic functions have been reported to be the clinical features of thalidomide-induced neuropathy.^[5,8,95] In a less severe form, these clinical findings might precede an irreversible neuropathy and could be used for monitoring against this eventuality. Electrophysiological testing such as measurement of sensory nerve action potential amplitudes at baseline and subsequently every 6 months have been suggested to detect an asymptomatic neuropathy.^[8]

Sural nerve biopsies of 4 patients experiencing a predominantly sensory type of thalidomide-induced neuropathy all demonstrated an increased number of unmyelinated axons per endoneural area.^[95] These changes were found to be independent

of patient age (range 54 to 76 years). The authors hypothesise that the numerical increase in small unmyelinated axons is related to regeneration following degeneration of unmyelinated axons.

The incidence of neuropathy seems to vary widely in different studies. In recent years, this adverse effect has frequently been reported in patients with AIDS receiving thalidomide, probably because there may be different potential risk factors for the development of neuropathy. However, there are only a few reports if neuropathy associated with the use of the drug in ENL^[4,49] or patients with advanced cancer.^[52-54,61,96,97] The observation that this complication may be related to cumulative dose^[4,79] emphasises the need of defined recommendations for monitoring, tapering and discontinuation. Because of the possibility for development of an irreversible neuropathy, patients should be carefully monitored and the drug should be immediately discontinued if there are positive findings. Special precaution will be required in patients with cancer who had been previously or currently exposed to neurotoxic chemotherapeutic agents such as cisplatin, etoposide, vinca alkaloids or taxanes.

4.4 Allergic Drug Reactions

Hypersensitivity symptoms such as rashes, eosinophilia, urticaria and related reactions are known to occur with some frequency in thalidomide-treated patients.^[4,8,28,49] These problems are reported to resolve with discontinuation but must be distinguished from the underlying disease of the patient, as well as from the often varied drug cocktail received because of the complex disease and symptom pictures of the patient receiving palliative care.

4.5 Haematological Effects

Lowered white blood cell counts, including neutropenia, have been observed in patients taking thalidomide, particularly patients with underlying disorders that may affect the haematological system.^[4,8,28,49]

4.6 Viral Load in HIV Infection

In the course of studying the effects of thalidomide on HIV-related diseases, it has been observed that viral load increased during drug administration.^[28] Further research is needed to confirm this observation, as it presents a possible source of concern when using thalidomide in any HIV-positive individual.

4.7 Drug Interactions

Thalidomide has been documented to enhance the sedative effect of barbiturates, alcohol (ethanol), chlorpromazine and reserpine.^[8] A difference could not be found in the use of oral contraceptives with and without coadministration of thalidomide.^[8] Potential interactions with other drugs including opioids have yet to be further characterised.

5. Future Research in Palliative Care Patients

The potential role of thalidomide within the field of palliative care has to be further determined. The main pathophysiological features of advanced cancer are metabolic abnormalities, cachexia, chronic nausea, insomnia and tumour-associated pain as well as decreased sensation of well-being. Perhaps the most intriguing property of thalidomide is its potential effect on many of these symptoms, and the fact that it is generally well tolerated in this very ill patient population.

Thalidomide appears to have significant effects on cancer cachexia, possibly due to a combination of immunomodulatory and CNS effects. To what extent thalidomide has anti-angiogenesis activity in certain types of cancer, and under which conditions, has yet to be elucidated. Clarification is required on whether thalidomide induces primary analgesia besides its possible secondary analgesia via an immunomodulation. Furthermore, recommendations for dosage and standardised monitoring are needed, and the dose-duration relationship has to be analysed.

New agents, acting at different levels, enrich the variety of possible therapies that may synergistically

address the mechanisms of cancer-related symptoms. Thus, prospective studies should investigate the use of thalidomide as a complementary component and evaluate possible drug interactions. The achievement of an optimal therapeutic effect for the patient without producing major adverse effects should be the goal.

In the patient with cancer, thalidomide-induced teratogenesis has limited relevance. Because of the usually short term treatment in patients with an extremely decreased life expectancy, neuropathy is less likely to occur and a possible mutagenic effect should not be a major concern. Despite the potential therapeutic benefits for selected patient populations, thalidomide is a drug with serious risks that cannot be ignored or taken lightly. Therefore, information, controlled distribution and regulation of the use of thalidomide are necessary. The thalidomide working group, formed by the FDA, continues to provide educational brochures to assist patients, clinicians and researchers.

We conclude that thalidomide has a number of interesting and promising effects on multiple clinical syndromes in patients with advanced cancer. These potential effects should be investigated. Because of its potentially wide availability and low cost, thalidomide might be particularly beneficial in many developing countries, some of which have been the most severely affected by the thalidomide teratogenesis catastrophe because of a high usage of the drug.

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References

1. Martindale W. The extra pharmacopoeia. London: Pharmaceutical Press, 1977
2. McBride WG. Thalidomide and congenital abnormalities [editorial]. *Lancet* 1961; II: 1358
3. Lenz W. Thalidomide and congenital abnormalities [editorial]. *Lancet* 1962; I: 45
4. Woodcock J. Supervisory review of NDA 20-785. Washington (DC): Food and Drug Administration, 1998
5. Thalidomide: potential benefits and risks: open public scientific workshop. Washington (DC): National Institutes of Health, 1997
6. Alstead S, MacArthur JG, Thomson TJ, et al. Clinical pharmacology. London: Baillire Tindall & Cassell, 1969
7. Wolstenholme G, Porter R, editors. Drug responses in man. Symposium on drug responses in man. London: Churchill, 1966
8. Link to Thalidomide's approved label: THALODMID (thalidomide) capsules. Washington (DC): US Food and Drug Administration/CTEP, 1998
9. Raje N, Anderson K. Thalidomide: a revival story. *N Engl J Med* 1999; 341: 1606-8
10. Celgene Corporation. Thalomid (thalidomide) STEPS (System for Thalidomide Education and Prescribing Safety) folder. Warren (NJ): Celgene Corporation, 1998
11. Lutwak-Mann C, Schmid K, Keberle H. Thalidomide in rabbit semen. *Nature* 1967; 214: 1018-20
12. Schumacher H, Smith RL, Williams RT. The metabolism of thalidomide: the fate of thalidomide and some of its hydrolysis products in various species. *Br J Pharmacol* 1965; 25: 324-37
13. Shannon EJ, Sandoval F, Krahenbuhl JL. Hydrolysis of thalidomide abrogates its ability to enhance mononuclear cell synthesis of IL-2 as well as its ability to suppress the synthesis of TNF-alpha. *Immunopharmacology* 1997; 36: 9-15
14. Bauer KS, Dixon SC, Figg WD. Inhibition of angiogenesis by thalidomide requires metabolic activation, which is species-dependent. *Biochem Pharmacol* 1998; 55: 1827-34
15. Zwingenberger K, Wendt S. Immunomodulation by thalidomide: systematic review of the literature and of unpublished observations. *J Inflamm* 1995; 46: 177-211
16. Sampaio EP, Sarno EN, Galilly R, et al. Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes. *J Exp Med* 1991; 173: 699-703
17. Moreira AL, Sampaio EP, Zmuidzinis A, et al. Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. *J Exp Med* 1993; 177: 1675-80
18. Rowland TL, McHugh SM, Deighton J, et al. Differential regulation by thalidomide and dexamethasone of cytokine expression in human peripheral blood mononuclear cells. *Immunopharmacology* 1998; 40: 11-20
19. Huizinga TW, Dijkmans BA, van der Velde EA, et al. An open study of pentoxifylline and thalidomide as adjuvant therapy in the treatment of rheumatoid arthritis. *Ann Rheum Dis* 1996; 55: 833-6
20. Moreira AL, Tsenova-Berkova L, Wang J, et al. Effect of cytokine modulation by thalidomide on the granulomatous response in murine tuberculosis. *Tuber Lung Dis* 1997; 78: 47-55
21. Sampaio EP, Kaplan G, Miranda A, et al. The influence of thalidomide on the clinical and immunologic manifestation of erythema nodosum leprosum. *J Infect Dis* 1993; 168: 408-14
22. Moller DR, Wysocka M, Greenlee BM, et al. Inhibition of IL-12 production by thalidomide. *J Immunol* 1997; 159: 5157-61
23. Haslett PA, Corral LG, Albert M, et al. Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8+ subset. *J Exp Med* 1998; 187: 1885-92
24. Zhu J, Deng GM, Diab A, et al. Thalidomide prolongs experimental autoimmune neuritis in Lewis rats. *Scand J Immunol* 1998; 48: 397-402
25. Nogueira AC, Neubert R, Helge H, et al. Thalidomide and the immune system. 3. Simultaneous up- and down-regulation of

- different integrin receptors on human white blood cells. *Life Sci* 1994; 55: 77-92
26. Neubert R, Nogueira AC, Neubert D. Thalidomide and the immune system. 2. Changes in receptors on blood cells of a healthy volunteer. *Life Sci* 1992; 51: 2107-16
 27. Haslett P, Hempstead M, Seidman C, et al. The metabolic and immunologic effects of short-term thalidomide treatment of patients infected with the human immunodeficiency virus. *AIDS Res Hum Retroviruses* 1997; 13: 1047-54
 28. Jacobson JM, Greenspan JS, Spritzler J, et al. Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group [see comments]. *N Engl J Med* 1997; 336: 1487-93
 29. Sampaio EP, Moraes MO, Nery JA, et al. Pentoxifylline decreases in vivo and in vitro tumour necrosis factor-alpha (TNF-alpha) production in lepromatous leprosy patients with erythema nodosum leprosum (ENL). *Clin Exp Immunol* 1998; 111: 300-8
 30. Goldberg RM, Loprinzi CL, Mailliard JA, et al. Pentoxifylline for treatment of cancer anorexia and cachexia? A randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 1995; 13: 2856-9
 31. Bruera ED, Roca E, Cedaro L, et al. Improved control of chemotherapy-induced emesis by the addition of dexamethasone to metoclopramide in patients resistant to metoclopramide. *Cancer Treat Rep* 1983; 67: 381-3
 32. Moertel CG, Schutt AJ, Reitemeier RJ, et al. Corticosteroid therapy of preterminal gastrointestinal cancer. *Cancer* 1974; 33: 1607-9
 33. Shannon EJ, Sandoval F. Thalidomide increases the synthesis of IL-2 in cultures of human mononuclear cells stimulated with Concanavalin-A, Staphylococcal enterotoxin A, and purified protein derivative. *Immunopharmacology* 1995; 31: 109-16
 34. Ostraat O, Riesbeck K, Qi Z, et al. Thalidomide prolonged graft survival in a rat cardiac transplant model but had no inhibitory effect on lymphocyte function in vitro. *Transplant Immunol* 1996; 4: 117-25
 35. Fernandez LP, Schlegel PG, Baker J, et al. Does thalidomide affect IL-2 response and production? *Exp Hematol* 1995; 23 (9): 978-85
 36. McHugh SM, Rifkin IR, Deighton J, et al. The immunosuppressive drug thalidomide induces T helper cell type 2 (Th2) and concomitantly inhibits Th1 cytokine production in mitogen- and antigen-stimulated human peripheral blood mononuclear cell cultures. *Clin Exp Immunol* 1995; 99 (2): 160-7
 37. Malaviya R, Ikeda T, Ross E, et al. Mast cell modulation of neutrophil influx and bacterial clearance at sites of infection through TNF-alpha. *Nature* 1996; 381: 77-80
 38. Gordon JR, Galli SJ. Mast cells as a source of both preformed and immunologically inducible TNF-alpha/cachectin. *Nature* 1990; 346: 274-6
 39. Dunzendorfer S, Schratzberger P, Reinisch N, et al. Effects of thalidomide on neutrophil respiratory burst, chemotaxis, and transmigration of cytokine- and endotoxin-activated endothelium. *Naunyn Schmiedeberg Arch Pharmacol* 1997; 356: 529-35
 40. D'Amato RJ, Loughnan MS, Flynn E, et al. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci U S A* 1994; 91: 4082-5
 41. Kruse FE, Jousen AM, Rohrschneider K, et al. Thalidomide inhibits corneal angiogenesis induced by vascular endothelial growth factor. *Graefes Arch Clin Exp Ophthalmol* 1998; 236: 461-6
 42. Gutman M, Szold A, Ravid A, et al. Failure of thalidomide to inhibit tumor growth and angiogenesis in vivo. *Anticancer Res* 1996; 16: 3673-7
 43. Lewis JJ. An introduction to pharmacology. Edinburgh: E. & S. Livingstone, 1960
 44. Barr Brown, RW, Hamilton-Hislop HG, Pritchard JG. A comparative clinical trial in the elderly of Distaval, Doriden, and Welldorm, three non-barbiturate hypnotics. *Br J Clin Pract* 1962; 16: 342-7
 45. Hoffman W, Grospietsch G, Kuhn W. Genital malformations in thalidomide-damaged girls. *Geburtsch u Frauenheilk* 1976; 36: 1066-70
 46. Eddy NB, Friebe H, Hahn KJ, et al. Codeine and its alternates for pain and cough relief. 2. Alternates for pain relief. *Bull World Health Organ* 1969; 40: 1-53
 47. Paulus W, Keymer R. Detection of contergan and doriden, especially in cadavers. *Arch Toxicol* 1963; 20: 38-43
 48. Horstmann W. Reference to central nervous system damage within the context of thalidomide embryopathy: pathologic-anatomic, electroencephalographic and neurologic findings. *Eur J Pediatr* 1966; 96: 291-307
 49. Iyer CG, Languillon J, Ramanujam K, et al. WHO co-ordinated short-term double-blind trial with thalidomide in the treatment of acute lepra reactions in male lepromatous patients. *Bull World Health Organ* 1971; 45: 719-32
 50. Sheskin J. Thalidomide in the treatment of lepra reactions. *J Clin Pharmacol Ther* 1965; 6: 303-6
 51. Murphy PG, Borthwick LS, Johnston RS, et al. Nature of the retrograde signal from injured nerves that induces interleukin-6 mRNA in neurons. *J Neuroscience* 1999; 19: 3791-800
 52. Marx GM, Levi JA, Bell DR, et al. A phase I/II trial of thalidomide as an anti-angiogenic agent in the treatment of advanced cancer [abstract 1751]. *Proc Annu Meet Am Soc Clin Oncol* 1999; 18: 454a
 53. Eisen T, Boshoff C, Mak I, et al. Continuous low dose thalidomide: a phase II study in advanced melanoma, renal cell, ovarian and breast cancer. *Br J Cancer* 2000; 82 (4): 812-7
 54. Long G, Vredenburgh J, Rizzieri DA, et al. Pilot trial of thalidomide post-autologous peripheral blood progenitor cell transplantation (PBPC) in patients with metastatic breast cancer [abstract 697]. *Proc Annu Meet Am Soc Clin Oncol* 1998; 17: 181a
 55. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 1999; 341: 1565-71
 56. Olson KB, Hall TC, Horton J, et al. Thalidomide (N-phthaloylglutamide) in the treatment of advanced cancer. *Clin Pharmacol Ther* 1965; 6: 292-7
 57. Minchinton AI, Fryer KH, Wendt KR, et al. The effect of thalidomide on experimental tumors and metastases. *Anticancer Drugs* 1996; 7: 339-43
 58. Browne WL, Wilson WR, Baguley BC, et al. Suppression of serum tumour necrosis factor-alpha by thalidomide does not lead to reversal of tumour vascular collapse and anti-tumour activity of 5,6-dimethylxanthone-4-acetic acid. *Anticancer Res* 1998; 18: 4409-13
 59. DiPaolo JA. Effect of thalidomide on a variety of transplantable tumors. *Cancer Chemother Rep* 1963; 29: 99-102
 60. Grabstald H, Golbey R. Clinical experiences with thalidomide in patients with cancer. *Clin Pharmacol Ther* 1965; 6: 298-302

61. Bruera E, Neumann CM, Pituskin E, et al. Thalidomide in patients with cachexia due to terminal cancer: preliminary report. *Ann Oncol* 1999; 10: 857-9
62. Gutierrez-Rodriguez, O. Thalidomide. A promising new treatment for rheumatoid arthritis. *Arthritis Rheum* 1984; 27: 1118-21
63. Waters MF. An internally-controlled double blind trial of thalidomide in severe erythema nodosum leprosum. *Leprosy Rev* 1971; 42: 26-42
64. Opromolla DV, Lima LS, Marques MB. Thalidomide in acute symptoms in leprosy (erythema nodosum or multiforme). *Hospital (Rio J)* 1966; 69: 827-44
65. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* 1995; 332: 1351-62
66. Shannon EJ, Miranda RO, Morales MJ, et al. Inhibition of de novo IgM antibody synthesis by thalidomide as a relevant mechanism of action in leprosy. *Scand J Immunol* 1981; 13: 553-62
67. Gehanno P, Barry B, Depondt J, et al. Mouth and pharyngeal hyperalgesic syndromes in AIDS. *Ann Otolaryngol Chir Cervicofac* 1990; 107: 311-3
68. Torras H, Lecha M, Mascaro JM. Thalidomide in the treatment of aphthosis and Behcet's disease. 4 years' experience. *Med Cutan Ibero Lat Am* 1982; 10: 103-12
69. Genov MF, Faure M, Thivolet J. Treatment of aphthosis with thalidomide and with colchicine. *Dermatologica* 1984; 168: 182-8
70. Klausner JD, Makonkawkeyoon S, Akarasewi P, et al. The effect of thalidomide on the pathogenesis of human immunodeficiency virus type 1 and M. tuberculosis infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996; 11: 247-57
71. Field EO, Gibbs JE, Tucker DF, et al. Effect of thalidomide on the graft versus host reaction. *Nature* 1966; 211: 1308-10
72. Rovelli A, Arrigo C, Nesi F, et al. The role of thalidomide in the treatment of refractory chronic graft-versus-host disease following bone marrow transplantation in children. *Bone Marrow Transplant* 1998; 21: 577-81
73. Vogelsang GB, Farmer ER, Hess AD, et al. Thalidomide for the treatment of chronic graft-versus-host disease. *N Engl J Med* 1992; 326: 1055-8
74. Chao NJ, Parker PM, Niland JC, et al. Paradoxical effect of thalidomide prophylaxis on chronic graft-vs.-host disease. *Biol Blood Marrow Transplant* 1996; 2: 86-92
75. Gutierrez-Rodriguez O, Starusta-Bacal P, Gutierrez-Montes O. Treatment of refractory rheumatoid arthritis: the thalidomide experience. *J Rheum* 1989; 16: 158-63
76. Wolkenstein P, Lатарjet J, Roujeau JC, et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet* 1998; 352: 1586-9
77. Sateia MJ, Silberfarb PM. Sleep. In: Doyle D, Hanks GW, Macdonald N, editors. *Oxford textbook of palliative medicine*. Oxford: Oxford University Press, 1998
78. Bruera E, Fainsinger RL, Schoeller T, et al. Rapid discontinuation of hypnotics in terminal cancer patients: a prospective study. *Ann Oncol* 1996; 7: 855-6
79. Politi P, Reboredo G, Lasso M, et al. Phase I trial of thalidomide in AIDS-related Kaposi sarcoma (ks) [abstract 161]. *Proc Annu Meet Am Soc Clin Oncol* 1998; 17: 41a
80. Neuenschwander H, Bruera E. Asthenia-cachexia. In: Bruera E, Higginson I, editors. *Cachexia-anorexia in cancer patients*. Oxford: Oxford University Press, 1996: 57-75
81. Billingsly KG, Alexander HR. The pathophysiology of cachexia in advanced cancer and AIDS. In: Bruera E, Higginson I, editors. *Cachexia-anorexia in cancer patients*. Oxford: Oxford University Press, 1996: 1-22
82. Gagnon B, Bruera E. A review of the drug treatment of cachexia associated with cancer. *Drugs* 1998; 55: 675-88
83. Fong Y, Moldawer LL, Marano M, et al. Cachectin/TNF or IL-1 alpha induces cachexia with redistribution of body proteins. *Am J Physiol* 1989; 256: R659-65
84. Plata-Salaman, CR, Borkoski JP. Interleukin-8 modulates feeding by direct action in the central nervous system. *Am J Physiol* 1993; 265: R877-82
85. Leon LR, White AA, Kluger MJ. Role of IL-6 and TNF in thermoregulation and survival during sepsis in mice. *Am J Physiol* 1998; 275: R269-77
86. Tamura S, Ouchi KF, Mori K, et al. Involvement of human interleukin 6 in experimental cachexia induced by human uterine cervical carcinoma xenograft. *Clin Cancer Res* 1995; 11: 1353-8
87. Pereira J, Bruera E. Chronic nausea. In: Bruera E, Higginson I, editors. *Cachexia-anorexia in cancer patients*. Oxford: Oxford University Press, 1996: 112-19
88. Traldi A, Vaccari GL, Davoli G. Use of imide of N-phthalyl-glutamic acid (thalidomide) in the symptomatic therapy of vomiting of many patients with malignant neoplasms or caused by administration of mechlorethamine HCl. *Cancro* 1965; 18: 336-41
89. Bruera E, Ernst S, Hagen N, et al. Effectiveness of megestrol acetate in patients with advanced cancer: a randomized, double-blind, crossover study. *Cancer Prev Control* 1998; 2: 74-8
90. Tisdale MJ. Inhibition of lipolysis and muscle protein degradation by EPA in cancer cachexia. *Nutrition* 1996; 12 Suppl. 1: S31-3
91. Maltin CA, Delday MI, Watson JS, et al. Clenbuterol, a beta-adrenoreceptor agonist, increases muscle strength in orthopaedic patients. *Clin Sci* 1993; 84: 651-4
92. Burman R, Chamberlain J. The assessment of nutritional status, caloric intake, and appetite in patients with advanced cancer. In: Bruera E, Higginson I, editors. *Cachexia-anorexia in cancer patients*. Oxford: Oxford University Press, 1996: 34-49
93. Dinarello CA, Wolff SM. Molecular basis of fever in humans. *Am J Med* 1982; 72: 799-819
94. Brendtzen KL, Baek D, Berild H, et al. Demonstration of circulating leukocytic pyrogen/interleukin 1 during fever [letter]. *N Engl J Med* 1984; 310: 596
95. Schroder JM, Gibbels E. Unmyelinated nerve fibers in senile nerves and in late thalidomide neuropathy: a quantitative electron microscopic study. *Acta Neuropathologica* 1977; 39: 271-80
96. Deaner P. Thalidomide for distressing night sweats in advanced malignant disease [letter]. *Palliat Med* 1998; 12: 208-9
97. Calder K, Bruera E. Thalidomide for night sweats in patients with advanced cancer [letter]. *Palliat Med* 2000; 14 (1): 77-8
98. Foley KM. The treatment of cancer pain. *N Engl J Med* 1985; 313: 84-95
99. Bruera E, MacMillan K, Hanson J, et al. The Edmonton staging system for cancer pain: preliminary report. *Pain* 1989; 37: 203-9
100. Ebadi M, Bashir RM, Heidrick ML, et al. Neurotrophins and their receptors in nerve injury and repair. *Neurochem Int* 1997; 30: 347-74
101. DeLeo JA, Colburn RW, Nichols M, et al. Interleukin-6 mediated hyperalgesia/allodynia and increased spinal IL-6 expression in a rat mononeuropathy model. *J Interferon Cytokine Res* 1996; 16: 695-700

102. Sommer C, Marziniak M, Myers RR. The effect of thalidomide treatment on vascular pathology and hyperalgesia caused by chronic constriction injury of rat nerve. *Pain* 1998; 74: 83-91
103. Ringheim GE, Burgher KL, Heroux JA. Interleukin-6 mRNA expression by cortical neurons in culture: evidence for neuronal sources of interleukin-6 production in the brain. *J Neuroimmunol* 1997; 63: 113-23
104. Bourde O, Kiefer R, Toyka KV, et al. Quantification of interleukin-6 mRNA in wallerian degeneration by competitive reverse transcription polymerase chain reaction. *J Neuroimmunol* 1999; 69: 135-40
105. Shin HC, Oh SJ, Jung SC, et al. Differential modulation of short and long latency sensory responses in the Si cortex by IL-6. *Neuroreport* 1997; 8: 2841-4
106. Rauen HM. Are thalidomide and its biological metabolites vitamin antagonists. *Arzneimittelforschung* 1963; 13: 1081-4
107. Felisati D. Teratogenic action of thalidomide. *Lancet* 1964; I: 724-5
108. Evered DF, Randall HG. Thalidomide and the B vitamins [editorial]. *Br Med J* 1963; 5330: 610
109. Rauen HM. Are thalidomide and its biological metabolites antagonists of glutamic acid. *Arzneimittelforschung* 1964; 14: 111-5
110. McColl JD, Globus M, Robinson S. An attempted reversal of thalidomide embryopathy in the rat by glutamine. *Can J Physiol Pharmacol* 1965; 43: 69-73
111. Furberg S. Structural relationship between thalidomide and nucleosides. *Acta Chem Scand* 1965; 19: 1266-7
112. Papst W. Thalidomide and congenital abnormalities of the eye. *Ber Deutsch Ophth Ges* 1964; 65: 209-15
113. Drugs and poisons in relation to the developing nervous system. Conference on drugs and poisons as etiological agents in mental retardation. Bethesda (MD): U.S. National Institute of Neurological Diseases and Blindness, 1967
114. Micks RH. The essentials of materia medica, pharmacology and therapeutics. London: J & A Churchill Ltd, 1965
115. Cant JS. Minor ocular abnormalities associated with thalidomide [letter]. *Lancet* 1966; I: 1134
116. Hirsch M. Chromosomal studies on so-called thalidomide embryopathy. *Med Klin* 1963; 58: 397-400
117. Bohm R, Nitsch K. Another chance for thalidomide [editorial]? *Lancet* 1966; I: 92
118. Jensen MK. Chromosome aberrations in human cells induced by thalidomide in vitro: preliminary report. *Acta Med Scand* 1965; 117: 783-4
119. Ashby J. Thalidomide is not a mutagen [letter]. *Nature* 1997; 389: 118
120. Smithells D. Does thalidomide cause second generation birth defects? *Drug Saf* 1998; 19: 339-41

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