# Thalidomide as a Teratogen

Before 1961, there was very little evidence for drug-induced malformations in humans. But in that year, Lenz and McBride independently accumulated evidence that a mild sedative, thalidomide, caused an enormous increase in a previously rare syndrome of congenital anomalies. The most noticeable of these anomalies was phocomelia, a condition in which the long bones of the limbs are absent (amelia) or severely deficient (peromelia), thus causing the resulting appendage to resemble a seal flipper (see Figure 1.16 in Gilbert, 2000). Over 7000 affected infants were born to women who had taken this drug, and a woman need only have taken one tablet to produce children with all four limbs deformed (Lenz, 1962, 1966; Toms, 1962). Other abnormalities induced by the ingestion of thalidomide included heart defects, absence of the external ears, and malformed intestines. The drug was withdrawn from the market in November, 1961.

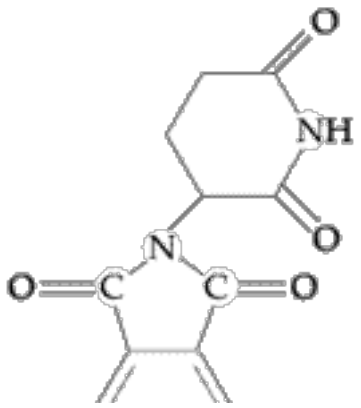

**Figure 1** The structure of thalidomide.

Nowack (1965) documented the period of susceptibility during which thalidomide caused these abnormalities. The drug was found to be teratogenic only during days 34-50 after the last menstruation (about 20 to 36 days postconception). The specificity of thalidomide action is shown in Figure 1.16B. From day 34 to day 38, no limb abnormalities are seen. During this period, thalidomide can cause the absence or deficiency of ear components. Malformations of upper limbs are seen before those of the lower limbs, since the arms form slightly before the legs during development.

The thalidomide tragedy showed the limits of animal models as tests of the potential teratogenic effects of drugs. Different species (and strains within species) metabolize thalidomide differently. Pregnant mice and rats–the animals usually used to test such compounds–do not generate malformed pups when given thalidomide. Rabbits produce some malformed offspring, but the defects are different from those seen in affected human infants. Primates such as the marmoset appear to have a susceptibility similar to that of humans, and affected marmoset fetuses have been studied in an attempt to discover how thalidomide causes these disruptions.

## The neural hypothesis

McCredie (1976a,b) proposed that thalidomide might

affect the differentiation of neural-crest-derived cells, and McBride and Vardy (1983) reported that the most noticeable difference in marmosets seen before limb malformations is the size of the dorsal root ganglia and their neurons. The number of neurons in these ganglia is markedly reduced. These authors speculate that the neurons from these ganglia are necessary for maintaining limb development and that thalidomide works by interfering with or destroying these neurons.

## The mesonephros hypothesis

A second mechanism to explain thalidomide teratogenicity has been advanced by Lash and Saxén (1972). Lash (1963) had noticed that the primitive kidney, the mesonephros, induced cartilage growth in cultured limb tissue. Lash and Saxén observed that thalidomide inhibited this mesonephros-induced cartilage growth in cultures of human organs obtained from electively aborted embryos. Moreover, radioactive thalidomide appeared to bind specifically to the human mesonephros.

## The angiogenesis hypothesis

It appears that thalidomide’s anticancer abilities stem from its interfering with angiogenesis. It has recently been shown (Joussen et al., 1999) that the teratogenicity of thalidomide and its related compounds correlates with its ability to block angiogenesis. Therefore, it is a distinct possibility that thalidomide acts in the embryo by inhibiting the

angiogenesis needed to make the limb. Neubert and colleagues (1995) and Geitz and colleagues (1996) have proposed that the initial target of thalidomide is the adhesion molecules of the limb bud and its capillaries. The addition of low doses of thalidomide to marmosets or to cultured endothelial cells results in the downregulation of several cell-cell and cell substrate adhesion molecules. A variant of this model was proposed recently by Stephens et al (2000). They propose that thalidomide interferes with the ability of insulin-like growth factor 1 (IGF-1) and fibroblast growth factor 2 (FGF-2) to stimulate the transcription of integrin subunit genes. The integrin is thought to be necessary to promote angiogenesis in the developing limb bud. They propose that thalidomide intercalates into the promoters of the IGF-1 and FCF-2 genes through the multiple GC boxes (GGGCGG) in their respective promoters. Intercalation into G-rich promoter regions of DNA would, therefore, block angiogenesis.

## Oxidative stress hypothesis

Parman and colleagues (1999) have found that thalidomide initiates embryonic DNA oxidation and teratogenicity, both of which are abolished by pre-treatment with the free radical spin trapping agent alpha-phenyl-N-t-butylnitrone (PBN). In contrast, in mice, a species resistant to thalidomide teratogenicity, thalidomide did not enhance DNA oxidation, even at a dose 300% higher than that used in rabbits. This may provide insight into why some species are susceptible to thalidomide and

others are not. These studies indicate that that the teratogenicity of thalidomide may involve free radical-mediated oxidative damage to embryonic cellular macromolecules.

The thalidomide tragedy also underscores another important principle: the metabolism of embryos is different from that of adults, and the construction of an organ can be affected by chemicals that have no deleterious effect on the normal functioning of that organ. Several medicines for adults are teratogenic to embryos. These include methotrexate (a drug used to stop tumor cell growth), anticonvulsants such as trimethadione and phenytoin, and anticoagulants such as warfarin. At present, we do not know the actual mechanism(s) by which thalidomide acts to inhibit limb or ear formation in human embryos. However, we are beginning to get some interesting hypotheses that can give us plausible answers.

The Thalidomide Victims of Canada have reprinted the brief history of the discovery of thalidomide teratogenicity, written by Dr. Lenz shortly before his death.

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