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THALIDOMIDE—A LESSON IN REMOTE EFFECTS OF DRUGS

In late January, 1962, my attention was attracted to reports of an outbreak of congenital malformations in children being born in Germany and its possible relation to a specific drug. Because of my interest in congenital malformations of the heart I decided to examine the situation myself. My trip was supported by grants from the International Society of Cardiology Foundation, the Heart Association of Maryland, and the National Institutes of Health. I traveled throughout West Germany with the exception of West Berlin. The results of this investigation seem to me so important and so pressing that I feel it my duty to report them to the medical profession without further delay.

The malformation with which I was concerned was phocomelia; the name comes from the Greek words *Phokos*, meaning seal, and *Melos*, meaning extremities. According to definition the development of the limb buds is so affected that the hands and feet arise from the trunk in a way suggestive of the flippers of a seal. Actually the injury affects the long bones of arms and legs; the hands and feet arise beyond the affected bone. In some instances the arms are rudimentary—4 such children are shown in Figure 1. The malformation involves both sides, but usually one side is more seriously affected than the other. The legs, too, may be affected. In 50% of the cases the arms only were affected, and in another 25% both the arms and legs are affected. At birth, a central hemangioma extending from the forehead over the nose to form a moustache on the upper lip is considered by Pfeiffer as characteristic of the syndrome. In some babies the external ear was absent. In the most severe cases malformation of the gut occurred accompanied by duodenal stenosis and anal atreasia, asplenia, and occasionally by a malformation of the heart. Mental retardation was found in only approximately 1%.

Phocomelia had long been known as a rare malformation. In 1959 a few cases were seen; these increased in 1960. By 1961 there was a veritable "epidemic" of phocomelia in Germany. Last November, Lenz suggested the possibility that the occurrence of the sudden outbreak of this malformation was connected with the use of a new sleeping tablet. The drug is known as thalidomide. It is a synthetic preparation whose chemical structure is shown in Figure 2. The drug was made by Grünenthal and marketed as Contergan in Germany, Distaval in the British Commonwealth, Softenon in Portugal, Kevadon (on trial in the U.S.A., but not released by the Food and Drug Administration), and Talimol in Canada. Thalidomide was also added to other medicines. The German drugs known as Algosediv, Peracon Expectorans, Grippex, and Polygripan all contain thalidomide, and so do the English drugs, Valgis, Tensival, Valgraine, and Asmaval.

The drug was invented by a German firm and first marketed during 1958; by 1960 it became Germany's most popular sleeping tablet and tranquilizer. The drug was sold without prescription until its long-continued use was found to cause polyneuritis; thereafter it was sold freely on prescription.

In November, 1961, W. Lenz in Hamburg (Germany) and W. G. McBride in Australia independently and almost simultaneously realized there was a close association between the new sleeping tablet and the outbreak of phocomelia. Both doctors reported their findings to their respective manufacturers in Germany and in Australia, and they also reported them to their Medical Societies. As soon as A. Spiers in Scotland heard these reports he checked his 10 recent cases of phocomelia with great care and obtained positive proof that 8 of the 10 mothers had taken Distaval. Thus, in three widely separated parts of the world, phocomelia occurred in the offspring of women who had taken thalidomide in early pregnancy.

The drug was withdrawn from the market at the end of November, 1961. Since then much circumstantial evidence of the relation between thalidomide and phocomelia has been collected. Lenz told me in March, 1962, that he had collected 50 cases of women with infants who have phocomelia in whom he knows the date of the last menstrual period (in about one-half of the instances the date of conception) as well as the date at which Contergan was taken, either as recorded on a hospital chart or a photostatic copy of the prescription. He found the sensitive period was between the 30th and 60th day after the last menstrual period; in most cases the drug had been taken between the 30th and 50th day. In the cases in which the date of conception was known the sensitive period was from the 28th to 42d day inclusive.

The sensitive period may be found to vary, and some women may prove to be immune, but the circumstantial evidence is overwhelming that the drug, if