Vandenbroucke JP. Thalidomide: an unanticipated adverse effect

Commentary on: McBride WG (1961). Thalidomide and congenital abnormalities. Lancet 2:1358.

Cite as: Vandenbroucke JP (2003). Thalidomide: an unanticipated adverse effect. The James Lind Library (www.jameslindlibrary.org). Accessed Monday 3 July 2006.

Author's contact details: Jan P Vandenbroucke, Department of Clinical Epidemiology, Leiden University Hospital, Leiden University Medical Center, CO-P, PO Box 9600, 2300 RC Leiden, The Netherlands.
Email: j.p.vandenbroucke@lumc.nl

On the 16 December 1961 The Lancet published a letter by an Australian obstetrician, William McBride. He reported that one out of every five women who had used a new drug to relieve morning sickness in early pregnancy had given birth to a severely malformed child: the babies lacked limbs. Two weeks earlier, the drug had been removed from the market in the UK. This marked the end of a devastating episode of detection and denial. Clinicians had been struck by this new and completely baffling abnormality, and had linked it to the new anti-emetic drug. McBride had been one of the first to see the association, as he had prescribed the drug liberally to pregnant women after being convinced of its value by a representative of the pharmaceutical firm that made it.

At about the same time, a German paediatrician, Widukind Lenz, had been struck by the multiple reports of babies born without limbs, several of them children of colleagues and acquaintances. One of the mothers of a malformed baby had developed tingling and weakness in her hands and feet while she was taking the drug, and this had set Lenz on the trail. He conducted a thorough epidemiological investigation, pinpointing the period of pregnancy associated with the greatest risk, and comparing the frequency of the birth defect for mothers who used the drug with the expected frequency in the general population. Both doctors warned the company. Still it took years for the company to give in; it was only after the disclosure of the reports in the popular press that a series of retractions from the market started. All this can be read in the book *Dark Medicine* (Stephens and Brynner 2001)

This dreadful episode has many lessons but one of them is that observant clinicians sometimes detect unanticipated effects of treatments. The reason that the unanticipated adverse effect of thalidomide was detected was that the abnormality was very striking visually: this birth defect was almost unheard of, but now frequently and strongly linked to the use of the new anti-nausea drug. Patients, too, sometimes identify a problem as a possible unanticipated effect of a drug. It was the mother of a young woman with a rare tumour of the vagina who suggested that her daughter's problem might be due to a drug - diethylstilboestrol (DES) that she - the mother - had been prescribed during pregnancy two decades earlier.

Sweeping changes in drug regulation resulted from the thalidomide disaster. Firstly, in the future, new drugs would be tested more extensively in animals to see if they passed the placenta. If a drug was not known to be safe during pregnancy, patient information leaflets issued with the drugs should say so. Secondly, the powers of national drug regulating authorities were greatly increased. Thirdly, several systems were set up to try to detect such side-effects at an earlier stage following release of the drug for marketing ("post marketing surveillance"). One of the systems of post marketing surveillance is the "Yellow card system" by which physicians can communicate their suspicions about possible side effects to regulatory authorities. Other systems require the study of groups of patients who have been prescribed a new drug in routine medical practice (see BMJ 1974). An overview of systems in use can be found in the *Oxford Textbook of Clinical Pharmacology* (Grahame-Smith and Aronson 2002).

References

Grahame-Smith DG, Aronson J (2002). Oxford textbook of clinical pharmacology and drug therapy. 3rd edition. Oxford: Oxford University Press.

Stephens T, Brynner R (2001). Dark medicine: the impact of thalidomide and its revival as a vital medicine. Cambridge, Mass: Perseus Publishing.