



British Society for the
History of Pharmacy

The evolution of pharmacy: Theme E, Level 3 **Adverse drug reaction reporting**



Early history

The fact that drugs might have effects on humans other than the ones intended has been known for many years. On 29 January 1848 a young girl called Hannah Greener was given an anaesthetic before treatment for an in-growing toenail. The anaesthetic was chloroform which had only been introduced a year earlier. Sadly Hannah died during the anaesthetic from what was thought to be an episode of ventricular fibrillation.

The incident received wide publicity, and as a result of continuing public and professional concern over anaesthetic safety *The Lancet* journal set up a commission which invited doctors throughout Britain and its colonies to report anaesthesia-related deaths. The results were published in 1893.

This was the forerunner of a spontaneous reporting system for suspected adverse drug reactions (ADRs). Unfortunately the system was neither retained for the reporting of anaesthesia-related deaths nor extended to the adverse effects of other drugs. Such a system had to wait until after the **thalidomide disaster** in 1961.

Awareness of side effects of drugs

The introduction of increasing numbers of potent drugs in the twentieth century began to expose the frequency and severity of adverse reactions. But the implications were not taken seriously by the authorities. As Leo Schindel, who in 1955 published the influential *Unexpected Reactions to Modern Therapeutics*, wrote:

“Until the 1930s there had been little need to worry about side effects. It was understood that an overdose might be lethal, but there was practically no such thing as an unexpected reaction to a particular medicament, except in those rare cases where the patient was hypersensitive to the substance.”

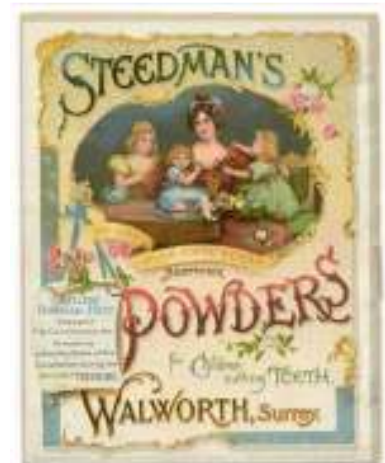
Yet during the 1930s, 1940s and 1950s increasing numbers of reports of adverse reports to drugs appeared in the medical press. In 1934 a large number of cases of agranulocytosis were reported in patients who had taken amidopyrine, which was a component of many patent medicines. As a result amidopyrine was moved to Schedule 4 of the Pharmacy and Poisons Act 1933 making it available only on prescription.

As soon as the sulphonamides were introduced in 1937 reports began to appear of unwanted side effects. The same was to happen following the introduction of penicillin, streptomycin and other antibacterials. These helped to raise awareness about the potential adverse effects of medicines. Reports relating to chronic mercury poisoning resulting from the use of teething powders first appeared in *The Lancet* in 1948. Such products were finally withdrawn in 1954.

Concerns before thalidomide

By the early 1950s concern about possible side effects and the inadequacy of testing was being raised by a number of physicians. Louis Meyler published his *Side Effects of Drugs* in 1952. Schindel's book followed in 1955.

In 1952 Dr George Discombe had an article published in the *British Medical Journal* warning about the inadequate testing of the many new drugs that were appearing. Between 1952 and 1960 nearly 1,000 new products came on the market, of which 118 were entirely new substances. His warnings were to go unheeded. In 1961 the thalidomide disaster drew attention to the failings of existing arrangements.





Adverse Drug Reaction reporting

The thalidomide disaster in 1961 prompted the UK government to set up a committee in 1962 to advise it on what measures were needed to ensure adequate safety testing and clinical trials of new drugs before general use, to ensure the early detection of adverse effects, and to keep doctors informed of issues. One of its recommendations was to establish a Committee on the Safety of Drugs (CSD). This was to be a voluntary scheme, working closely with the pharmaceutical industry to look at toxicity tests, clinical trials, efficacy and adverse reactions during general use.

The highly-regarded first chairman of the CSD, Sir Derrick Dunlop, wrote to all doctors on 4 May 1964 asking for their help in setting up a scheme "to report promptly details of any untoward condition in a patient which *might* be the result of drug treatment". This spontaneous adverse reaction reporting scheme was based upon such reports through reply-paid yellow cards and became popularly known as the "Yellow Card Scheme". In the first year, up to 100 reports were received each week.

Further development of the scheme

The Committee on Safety of Medicines (CSM) was set up as a result of the Medicines Act 1968 and took over responsibility for monitoring adverse drug reactions from the CSD. The CSM adopted a new version of the yellow card in 1971 so as to provide more information to help analysis. As a result of the scheme, the eye damage induced by the anti-hypertensive practolol was identified in 1976, and the fact that benoxiprofen caused jaundice and fatalities in the elderly identified in 1982.

To improve the rate of reporting of adverse reactions a "black triangle" symbol was launched in 1975 to highlight to prescribers recently-introduced products for at least two years after marketing. This mark applied to new medicines, new combinations of existing medicines, medicines with a new route of administration, medicines with a significant new indication, and new types of formulation for that medicine.

Extension beyond doctor reporting

The scheme was originally restricted to doctors. It was extended to hospital pharmacists in 1997, and from 1999 all community pharmacists in the UK were allowed to report adverse drug reactions. The scheme was later extended to include reporting by all nurses, health visitors and midwives.

A pilot scheme to allow patients to report their experiences was introduced in 2005. Following a three year trial, the scheme was permanently expanded to include members of the public in February 2008. Anyone in the UK, patient or healthcare professional, can now report an adverse reaction to a medicine either on a paper form or online on the MHRA's website; patients can also report reactions by telephone.

FIND OUT MORE

Links to other sheets:

Theme E, Level 1: The control of harmful substances

Theme E, Level 2: The history of UK medicines regulation

Further reading:

Applebe, Gordon E.; From arsenic to thalidomide: a brief history of medicine safety, (Making Medicines 243-260 Pharmaceutical Press, London, 2005).

Cox, Anthony, Yellow card reporting scheme: what to report and where to? (Tomorrow's Pharmacist, 2005, 66-67).

Griffin, John P, *The evolution of human medicines control from a national to an international perspective*, (Adverse Drug React. Toxicol. Rev. 1998, 17(1) 19-50 Oxford University Press).

Shah, R R, *Thalidomide, drug safety and early drug regulation in the UK*, (Adverse Drug React. Toxicol. Rev. 2001, 20(4) 199-255 Oxford University Press).