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PHARMACOVIGILANCE

# The history of pharmacovigilance

**Jacques Caron, Michaël Rochoy, Louise Gaboriau, Sophie Gautier***

*Centre régional de pharmacovigilance, CHRU de Lille, 1, place de Verdun, 59045 Lille cedex, France*

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**Summary** This article reviews the main historical events before the 21st century and explained their consequences in the current pharmacovigilance legislation.



## Abbreviations

| | |
|---|---|
| AFSSAPS | French Agency for the Safety of Health Products (*Agence française de sécurité sanitaire des produits de santé*) |
| CAST | Cardiac Arrythmia Suppression Trial Study |
| DES | diethylstilbestrol |
| FDA | Food and Drug Administration |
| PVC | Premature ventricular contractions |

Unlike the history of medicine, the history of pharmacovigilance is fairly recent. Even if it is important to point out physicians' bygone preoccupations with adverse drug reactions, illustrated in Hippocrates' ''*primum non nocere*'', the birth and development of pharmacovigilance occurred at a later stage and progressively. This evolution came about

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* Corresponding author.
*E-mail address:* sophie.gautier@chru-lille.fr (S. Gautier).

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This fact, I am aware, has been proved by means of statistics, and we all know that statistics occasionally lead to erroneous conclusions in the abstract; but they are the best means we have of forming an approximately correct idea, coupled with an individual recollection of some hair-breadth escapes and fatal terminations resulting from the use of chloroform; and the following statistics, which were proved by the late Professor Morgan of Dublin to be correct, show the relative danger of each agent.

| | Deaths. | Inhalations. |
|---|---|---|
| Ether | 4 to | 92,815 or 1 in 23,204 |
| Chloroform | 53 to | 152,260 or 1 in 2,873 |
| Mixture of chloroform and ether | 2 to | 11,176 or 1 in 5,558 |
| Bichloride of methylene | 2 to | 10,000 or 1 in 5,000 |
| Nitrous oxide | Not given. | |

From the above table, we learn two facts: 1. That chloroform is the most dangerous anæsthetic (of those in ordinary employment) that we could use; 2. That ether is about eight times safer, and proved by the same table to be the safest of all anæsthetics used in prolonged operations.

**Figure 1.** Extract from Ormsby's article, published in the *British Medical Journal* in 1877, showing the incidence of deaths in presence of chloroform and ether. With courtesy *British Medical Journal* [2].

through problems of pharmacovigilance, debates and ''scandals'' that appeared in the 19th century, some of which led to legislation in order to protect patients whilst reinforcing the prerogatives and demands, in terms of safety, of national or supranational agencies that had been set up. Outlining the history of pharmacovigilance requires certain issues representative of the main stages in the history of drug safety to be broached, whilst other problems, mentioned here very briefly but often not even mentioned at all, were nonetheless major events in terms of human consequences.

The first example of a safety issue that led to coordinated and rational pharmacovigilance reflection is provided by chloroform, discovered in France by Eugène Soubeiran in 1831 (this authorship has however been contested by the Germans). While the very first general anaesthetic was carried out publicly with ether by William Morton in Boston in 1846, chloroform was first used as an obstetrical anaesthetic in Edinburgh in 1847 by James Young Simpson. Chloroform shot to fame a few years later when Queen Victoria underwent anaesthesia with the substance for the birth of her eighth child in 1853. The use of chloroform spread and even supplanted ether, especially in Britain and France. However, from the first years following its use, attention was drawn to fatal accidents in the form of syncope, known as ''chloroform-induced syncope''. Because deaths had also been reported with ether and because of the growing concern of both the general public and physicians, *The Lancet* set up a commission inciting doctors from the United Kingdom and its colonies to report any deaths related to general anaesthesia, collecting the data and publishing the results in 1893 [1]. This first example of a requested notification, associated with incidence estimations [2] which gave chloroform a clear disadvantage compared to ether (Fig. 1), led to the first descriptions, forty years later, of deaths linked to chloroform and ultimately to its demise in favour of ether.

The second significant problem occurred later and stemmed from acetylsalicylic acid. We know that Felix Hoffman (Fig. 2), a German chemist working for Bayer, synthesised acetylsalicylic acid on August 12th 1897, which was better tolerated when ingested than sodium salicylate, and was given the name Aspirin (the French have fought for its authorship against the Germans, which is only fair after what was mentioned earlier). What is less known is that within two weeks, in August 1897, Felix Hoffman synthesized Aspirin and (re)synthesized diacetylmorphine (a.k.a. Heroin), the discovery of which went unnoticed, and was attributed in 1874 to a British chemist, Charles Adler Wright (with no authorship dispute to this day, neither by the French nor by the Germans). The Bayer Laboratory studied the effects of diacetylmorphine on an experimental level as well as on patients with tuberculosis, who found the drug remarkably efficacious and powerful. No addictive potential was found at that time. Enthused by the results, the managers of Bayer Laboratories thought that diacetylmorphine should be medically ranked alongside ''heroic remedies''; they therefore gave it the name Heroin® and marketed it in 1898, one year before Aspirin, as an antitussive and analgesic drug. Commercial success was fast (we can well imagine), especially as it was supported by a large advertising campaign. However, the addictive power of Heroin unavoidably came to be recognized. In the end, hundreds of thousands of people were found to have become dependant on the drug at the beginning of the 1910s (a number of 500,000 dependant patients was reported in the US!). The first steps to limit the medical use of this drug were taken in 1912 and Bayer Laboratory stopped its production of heroin in 1913. However, the recreational use of heroin, which has been well established since that time, unfortunately continues to wreak havoc across the world.

Leaving the 19th century behind, we can now look at what happened in the 20th century. Sulfanilamide has been synthesized since 1908 but it was not until 1935 that a team from the Institut Pasteur demonstrated that this product was actually the active, colourless sulfonamide metabolite, sulfamidochrysoïdine (Prontosil®), a sulfonamide azoic dye, initially intended for carpet dyes, but for which Gerhard Domagk (Nobel Prize for Medicine in 1939) identified antistreptococcal properties. Although it was put on the market in the form of pills or capsules in the US, the commercial development of sulphanilamide led a small Tennessee company (SE Massengil & Co.) to solubilize the product into diethylene glycol and to market Elixir Sulfanilamide® in 1937, without any toxicological testing being carried out. Very quickly a link was established between a series of deaths from kidney failure and the marketing of this new pharmaceutical form of sulfanilamide involving the responsibility of a solvent.

A batch recall campaign was organised on a large scale by the Food and Drug Administration (FDA), created in 1906, thus minimizing the consequences of this tragedy, responsible however for the deaths of 105 people, including 34 children [3]. What is important to remember is that the FDA did not have the power at that time to recall products for safety reasons, and that the only legal leverage they had was that the brand name ''Elixir'' was only used for speciality products containing alcohol, which was not the case for Elixir Sulfanilamide®. Without this expedient, which enabled the recovery of 228 gallons of Elixir out of 240 before distribution (Fig. 3), the number of deaths would have been much greater. A year later, in 1938, President Franklin Roosevelt signed the ''Federal Food, Drug and Cosmetics Act'', which included in the law the necessity for pharmaceutical companies to submit a report to the FDA concerning the safety of all medicinal drugs. It was the first time that safety data