Memory can save lives

The withdrawal of Mediator° (*benfluorex*) from the French market in 2009 owes a lot to the connections made with past disasters. Healthcare professionals remembered the damage associated with other amphetamine-like appetite suppressants – *aminorex* in the 1960s and *dexfenfluramine* (Isomeride°), which is chemically related to Mediator°, in the 1990s (1,2). In 1997, marketing of certain amphetamines, including *dexfenfluramine*, was stopped because the serious heart valve disease in exposed patients reminded physicians in the United States of the damaged valves, seen years if not decades earlier, caused by rye ergot derivatives (2).

Human memory can save lives. On the other hand, failure by regulatory agencies and companies to remember the past exposes patients to preventable harms.

In 2015, the US Food and Drug Administration (FDA) announced that it had received reports of diabetic ketoacidosis or ketosis attributed to the gliflozin group of hypoglycaemic drugs, such as *dapagliflozin* (Forxiga°), marketed in France in 2020 for diabetic patients (see pp. 262-263 of this issue) (3).

This announcement appeared to be unexpected, whereas it actually concerned an adverse event that was predictable, if historical knowledge had been recalled. Ketoacidosis had in fact been reported for the first time 125 years ago with phlorizin, a naturally-occurring substance which inhibits, in particular, the sodium-glucose cotransporter-2 (SGLT2) and which served as a model for the development of the gliflozins (4).

As early as the end of the 19th century, the German physician Josef von Mering reported that ketoacidosis had occurred with phlorizin during his research on antipyretics (4). Observations published in English appeared as of 1914 in widely read journals such as *JAMA* or the *American Journal of Physiology* (4,5). The topic was discussed at the first annual meeting of the American Diabetes Association in 1941 (4).

Is the past forgotten through a lack of curiosity, a lack of astuteness or a lack of methodological rigour? Or simply because of the difficulty of accessing the oldest archives? Pre-1963 publications were not in fact digitised in the Medlars database (the forerunner of Medline) (5). Whatever the reason, in the case of gliflozins, the opportunity to make use of already established knowledge was missed, both during the development of these drugs by companies, and during the analysis of their evaluation prior to marketing authorisation (4).

In the field of pharmaceuticals, novelty is not always what it seems. It is often useful to look for relationships between substances in order to predict certain beneficial or adverse effects. Digitisation of publications, including very old ones, would make such research easier.

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EDITORIAL