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Aspirin and Reye's Syndrome

Discovery of Aspirin and Paracetamol

In a recent article, Orlowski et al.[1] suggest that aspirin (acetylsalicylic acid) is not a cause of Reye's syndrome.[1] In describing historical aspects of Reye's syndrome, the authors mistakenly date the discovery of aspirin to 1899 and paracetamol (acetaminophen) to 1955.[1]

The medical application of salicylates dates back thousands of years, with the use of leaves (and later, bark) from the willow tree (reviewed in Jack[2] and Mackowiak[3]). Chemists in the early 19th century discovered that the active component of willow extract was the glycoside salicin, which could be hydrolysed and further manipulated to yield salicylic acid.[2,3] Salicylic acid and its sodium salt, however, were quite unpalatable and toxic (particularly to the stomach), prompting a search for alternative pharmaceuticals.

This effort led to the synthesis of acetylsalicylic acid by Gerhardt in 1853 by reacting sodium salicylate with acetyl chloride.[2,4-6] Gerhardt's synthesis was difficult and the yield impure and unstable, prohibiting its adoption as a replacement for salicylic acid.[2,6] In 1897, however, Dreser and Hoffman made a stable preparation of acetylsalicylic acid for Friedrich Bayer and Co. in Germany,[7] leading to the widespread release of 'aspirin' in 1899.[2,3]

Paracetamol, unlike aspirin, was not developed from a botanically derived antipyretic substance. This compound (N-acetyl-*p*-aminophenol) is rooted in the German aniline dye industry (reviewed in Spooner and Harvey[8] and Roberts and Morrow[9]). In 1886, the acetylated aniline compound acetanilide was inadvertently discovered to be an effective antipyretic and analgesic medication, and was introduced into clinical medicine as antifebrin by Cahn and Hepp.[5,8,10] This compound, however, was withdrawn from use because of toxicity.[8]

Efforts to produce safer antipyretics led to the development of the acetanilide derivatives, phenacetin (1887) and paracetamol (1893) by von Mering.[11] He favoured the safety profile of phenacetin over paracetamol, leading to the popular clinical use of the former drug for nearly 80 years.[12] Not until the late 1940s was it discovered that paracetamol was the major metabolite of phenacetin and was less toxic than the parent compound,[13] resulting in the re-emergence of paracetamol in the mid1950s.

Despite the long history of their medicinal use, we continue to develop a deeper understanding of the mechanisms of action and adverse effects of antipyretic drugs such as aspirin and paracetamol.[14] The compelling piece by Orlowski et al.[1] contributes to this pursuit.

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