

## ADVERSE DRUG REACTIONS OF PHENAZONE: KNOWLEDGE FROM BOOKS AROUND 1900 COMPARED TO TODAY'S SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The first book on adverse drug reactions (ADR), "Die Nebenwirkungen der Arzneimittel" by Louis Lewin (1850–1929), was edited in 1881. Another German work on side effects was composed by Otto Seifert (1853–1933) in 1915. In 1909, a book by Lyman Frederick Kebler (1863–1955) on the harmful effects of acetanilide, antipyrine, and phenacetin was edited in the USA. These three books were published in a time when the first synthetic active ingredients entered the market as drugs on an industrial scale. Phenazone, synthesised for the first time in 1883, is an early representative of a synthetic pain-relief and anti-inflammatory substances. Phenazone is currently sold in the proprietary medicinal product Migränin® 500 mg. The licence holder is obliged to publish the side effects in the standardised form of expert information. This study is to compare Lewin's, Seifert's and Kebler's knowledge on the side effects of phenazone with the side effects of Migränin® 500 mg that are mentioned in the current Summary of Product Characteristics.

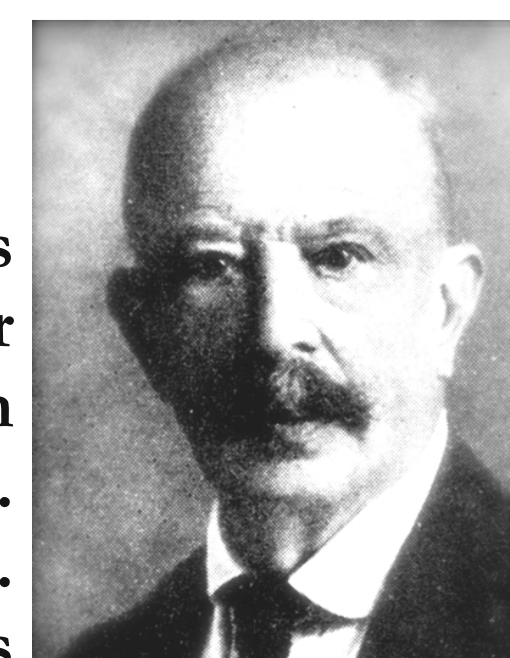
ICD-10-WHO Version 2011	ADR	Lewin 1899	Seifert 1915	Kebler 1909	Phenazone SPC 2008
Diseases of the blood and the blood-forming organs, and certain disorders involving the immune system	Alteration in the blood formation				✓
Diseases of the digestive system	Nausea or vomiting	Feelings of disgust ✓	Feelings of disgust Abdominalgia Hematemesis ✓	Digestive tract with abnormal symptoms ✓	Nausea and vomiting ✓
Diseases of the skin and the subcutaneous tissue	Rash	Antipyrin rash ✓ Antipyrin pemphigus Heavy stomatitis Blemishes on the buccal and labia mucosus membrane Bloated face Gangrene after injection Antipyrin fever	Antipyrin eruption or enanthem ✓ Fixed drug eruption Ulceration membranous stomatitis Erythema exsudativum multiforme Measles like rash Black stain of the penis skin	Urticaria ✓ Rash Itching	Fixed rash, urticaria ✓ Inflammation and swelling of the mucosa Blemishes and blebbing Erythema multiforme Erythema nodosum Angioedema Toxic epidermal necrolysis
Injuries, poisoning and certain other consequences of external causes	Allergic reaction	Curious excitation ✓ Freezing Dyspnoea Collapse	Hypersensitivity to Antipyrin ✓ Abnormal chills Cardiac disorders Vertigo Collapse	Coldness of the extremities ✓ Rapid and feeble pulse Collapse Vertigo	Shock symptoms ✓ Cold perspiration Dyspnoea Uneasiness in the cardiac region Vertigo Drop in blood pressure
Diseases of the eye and adnexa	Temporary to entire blindness	✓	✓	✓	
Diseases of the nervous system	Epilepsy, convulsions	✓	✓	✓	
Mental and behavioural disorders	Apathy, presyncope	✓	✓	✓	
					Key: ✓: correlation in all sources ✓: correlation in single sources

### LOUIS LEWIN



Louis Lewin was born on 9<sup>th</sup> November 1850 in Tuehel (West Prussia). In 1856, the family moved to Berlin. Lewin learned German from books. From 1864, he visited the Friedrichwerdersche Gymnasium. Afterwards Lewin entered the Friedrich Wilhelm University in Berlin to study medicine in 1871. Here, he completed his doctorate in 1875 with a thesis on the effect of aconitine on the heart. He gained his licence to practice medicine in 1876. Two years later, he accepted a position as an assistant to Oskar Liebreich at the Pharmacological Institute of the University of Berlin. Lewin completed his post-doctoral studies in 1881 in pharmacology and toxicology. In 1894, he was appointed titular professor. In 1919, he became an honorary professor at the Technical University in Berlin. On 1<sup>st</sup> December 1929, Lewin died. In addition to pharmacological and toxicological issues, he worked on legal, hygienic and social-medical problems. His most important publications include: "Die Nebenwirkungen der Arzneimittel" (Berlin 1881; 2<sup>nd</sup> edition 1883; 3<sup>rd</sup> edition 1899), "Lehrbuch der Toxicologie" (Vienna 1895; 2<sup>nd</sup> edition 1897). Furthermore, he published works on investigations of inorganic substances, natural substances and anatomy.

### OTTO SEIFERT



Otto Seifert was born on 9<sup>th</sup> December 1853 as the son of a clergyman in Bimbach in Lower Franconia. Seifert attended the Latin school in Winsbach and the grammar school in Ansbach. He studied medicine in Würzburg and Erlangen. In 1877, Seifert gained his doctorate. Two years later, he went to Vienna to train in rhinolaryngology, otology and dermatology. From May 1879, Seifert worked in Sommershausen near Würzburg as the local doctor. A year later, he accepted a post as medical assistant at the Juliuspital near Würzburg. Here, he was given the opportunity to hold courses in laryngoscopy. As early as the winter semester 1881, he had 46 students. In 1883, Seifert completed his post-doctoral studies in internal medicine. In 1887, he was appointed lecturer in skin and venereal diseases, and continued to hold courses in rhinolaryngology. In May 1905, the Royal University Polyclinic was opened specifically for rhinolaryngology. On 16<sup>th</sup> September 1906, Seifert was appointed an extraordinary professor for skin and venereal diseases and for rhinolaryngology. In 1919, Seifert became an emeritus professor because of a bilateral ear disorder. Otto Seifert died 10<sup>th</sup> February 1933. Seifert published 87 publications on rhinolaryngology. He also supervised 69 dissertations from his clinic and contributed to textbooks and manuals.

### LYMAN FREDERICK KEBLER



Kebler was born on 8<sup>th</sup> June 1863 in Lodi Township. After High School in Ypsilanti, he attended the college of Pharmacy at the University of Michigan until 1890. Then Kebler studied chemistry. He completed his bachelor's degree in 1891, and his master's followed a year later. In 1893, Kebler worked for the wholesaler Smith, Kline & French Co. in Philadelphia. There, he set up a chemical-analytical department. Its task was the development of methods for uncovering counterfeit drugs and counterfeit foodstuffs. At the same time, he was studying medicine at Jefferson Medical College and subsequently at Temple University. In 1894, Kebler entered the American Public Health Association. Here, he worked on the creation of analytical standards in the USP. In 1902, Kebler led the U.S. Drug Laboratory. The methods developed there for uncovering counterfeit drugs and impurities were incorporated into the "Pure Food and Drug Act" issued in 1906. From 1910 to 1920, he was elected to the USP Committee of Revision. Between 1920 and 1930, he acted as the convention secretary. Lyman Frederick Kebler died in Washington on 4<sup>th</sup> March 1955 at the age of 91.

## RESULTS

For the evaluation of the results, the side effects are organised in a table, classified by source in the System for the International Statistical Classification of Diseases and Related Health Problems (ICD-10-WHO). According to this classification, phenazone is subject to side effects in the following categories:

1. Diseases of the blood and the blood-forming organs, and certain disorders involving the immune system,
2. Mental and behavioural disorders,
3. Diseases of the nervous system,
4. Diseases of the skin and the subcutaneous tissue,
5. Diseases of the digestive system,
6. Diseases of the eye and adnexa,
7. Injuries, poisoning and certain other consequences of external causes.

From the table it is clear that Lewin, Seifert, Kebler and today's product information consistently mention side effects in the categories:

1. Diseases of the skin and subcutaneous tissue,
2. Diseases of the digestive system,
3. Injuries, poisoning and certain other consequences of external causes.

In comparison with the other categories, most side effects could be classified here. Thus, it is possible to establish that the vast majority of undesired side effects of the drug, with the exception of an alteration in the blood formation, were already known at the end of the 19<sup>th</sup> century. In addition to the consistencies, Lewin, Seifert and Kebler mention side effects which are not mentioned in the product information today. These can be assigned to the categories:

1. Diseases of the eye and adnexa,
2. Diseases of the nervous system,
3. Mental and behavioural disorders.

Lewin, Seifert and Kebler specify temporary to complete blindness, epileptic seizures, convulsions, delirium. Lewin puts many of the side effects down to the quality of the antipyrine. He criticises "the poor quality of the antipyrine" or the fact that "a dishonest distributor had badly handled" the drugs. Possible reasons for the quality deficiencies that he expressed may be impurities of the drug, for example due to by-products of the phenazone synthesis, or counterfeits. Interaction with other drugs that were taken is also possible, but is not mentioned by Lewin, Seifert and Kebler.