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The evil of the unknown - risk-benefit evaluation of new synthetic drugs in the 19th century

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In the 19th century, synthetic chemistry discovered completely new chemical entities for medicinal use, which dramatically enriched the therapeutic armamentarium. However, no information was available regarding the safety of these new drugs, which were unrelated to most of the medicinal agents formerly known. Therefore, the question arises, if and how far, considerations regarding the relationship between benefit and risks were made. In this study, chloroform, phenazone (antipyrine) and sulfonal, were investigated as examples for drugs newly introduced in the 19th century. The results revealed that these drugs were provided by the manufacturer, tested by the physicians in a multicentre pattern and side effects were published in the medical literature soon after. Within a few years, several hundred cases were reported but the data were rarely summarized statistically. Therefore, physicians needed to stay updated with the medical literature because neither systematic industrial research nor regulatory authorities existed. The number of case reports within the first years were sufficient to detect common (> 1/100 to < 1/10) side effects but rare events were also reported. An extraordinary example is the drug-induced toxic epidermal necrolysis, which is commonly known as the Lyell syndrome or its less severe form, the Stevens–Johnson syndrome. This reaction has been clearly described by Baruch Spitz (1854–1932) as a side effect of antipyrine in 1887, several decades before Stevens, Johnson and particularly Lyell.

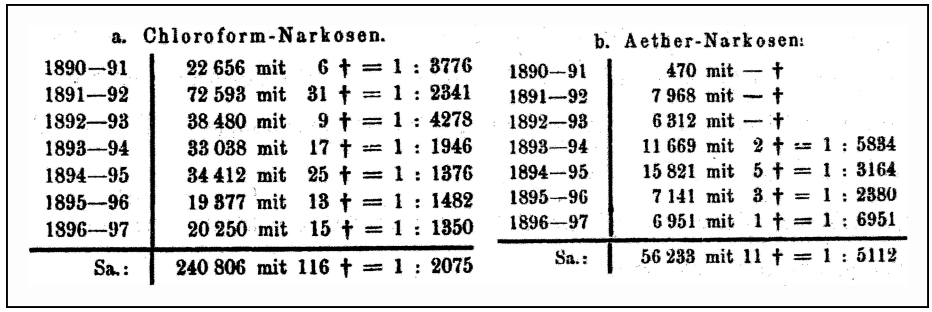
1. Introduction

In the 19th century, pharmacotherapy fundamentally changed because more chemical substances that were not associated with natural compounds were synthesised as therapeutic agents. Naturally-derived products or compounds have at least some toxicity and efficacy information available (Helmstädter and Staiger 2014); however, these novel therapeutic agents did not have natural prototypes and this created new challenges in their drug safety evaluation. For example, the alkaloids which were isolated from well-known medicinal plants, and metallic compounds such as mercury or antimony had been the subject of benefit-risk evaluations for centuries (Sneader 2005; Hickel 2008). Since the mid-18th century, the term 'Nebenwirkungen', which is German for adverse drug reactions, has been used in several publications (e.g. Zimmermann 1767). This suggests that physicians knew as early as the mid-18th century that drug therapy also caused side effects. Since the 19th century, several studies have investigated the adverse effects of drug therapy using systematic approaches (Lewin 1881). However, with the advent of newly created chemicals people were unable to rely on common or traditional knowledge. Thus, in this context the question arises, if and how far, suggestions regarding the benefit-risk relationship were made by physicians using formerly unknown chemical entities the first time for human treatment. In this study, chloroform, phenazone (antipyrine) and sulfonal, which are three synthetic compounds without natural prototypes, were investigated. Since 1847, chloroform was used as a narcotic while phenazone (antipyrine) was patented as an analgesic and antipyretic in 1883 and sulfonal was introduced as a hypnotic compound in 1888. Since archive material from the manufacturers was hardly available, the investigations presented here are based on a systematic screening of publications in leading German medical journals, the primary place of knowledge exchange about new pharmaceutical substances in the 19th century.

2. Investigations and results

2.1. Chloroform

Chloroform was synthesized independently by Samuel Guthrie (1782–1848), Eugène Souberain (1797–1858) and Justus von Liebig (1803–1873) in the US, France and Germany, respectively (Sneader 2005; Keys 1968). In 1847, the British gynaecologist James Simpson (1811–1870) initially tested the substance on himself and two colleagues that volunteered to evaluate the drug. Dr. Simpson discovered the narcotic properties of chloroform, used it in 50 clinical cases and published the results that same year (Simpson 1847). In January 1848, the first chloroform fatality occurred when it was used in anaesthesia. A young girl died while she was having surgery on her toe (Matsuki and Zsigmond 1975). A second fatality was published three months later (Selby 1848). These deaths initiated a discussion about the risks of chloroform as an anaesthetic, mainly in comparison to ether, the other narcotic that was commonly used. In



a. Chloroform-Narkosen.

1890—91	22 656 mit	6 †	= 1 : 3776
1891—92	72 593 mit	31 †	= 1 : 2341
1892—93	38 480 mit	9 †	= 1 : 4278
1893—94	33 038 mit	17 †	= 1 : 1946
1894—95	34 412 mit	25 †	= 1 : 1376
1895—96	19 877 mit	13 †	= 1 : 1482
1896—97	20 250 mit	15 †	= 1 : 1350
Sa.:	240 806 mit	116 †	= 1 : 2075

b. Aether-Narkosen:

1890—91	470 mit	— †	
1891—92	7 968 mit	— †	
1892—93	6 312 mit	— †	
1893—94	11 669 mit	2 †	= 1 : 5834
1894—95	15 821 mit	5 †	= 1 : 3164
1895—96	7 141 mit	3 †	= 1 : 2380
1896—97	6 951 mit	1 †	= 1 : 6951
Sa.:	56 233 mit	11 †	= 1 : 5112

Fig. 1: Chloroform fatalities in comparison to ether published by Gurlt (1897).

Britain, 'chloroform committees' were established to evaluate the new substance and give recommendations for its use (Myles 2010). The 'chloroform committees' preferred ether because the Irish Surgeon John Morgan published preliminary statistics that suggested the calculated death risk for chloroform, ether or a mixture of both was 1:2.873, 1:23.204 and 1:5.888, respectively (Morgan 1872). While the death risk for chloroform was approximately tenfold higher than the death risk for ether, chloroform was still the preferred anaesthetic. This preference was due to both the patients and the physicians. Patients favoured chloroform because it did not smell as bad as ether while physicians preferred it because it was much easier to administer. Morgan's assessment did not take into consideration the physical danger associated with applying the highly explosive ether under gas lighting or in cases of cautery. In Germany, the risks of chloroform and ether as anaesthetics were also intensely discussed with arguments frequently appearing in published journal articles and conference reports (for details see Schneider 2014). Statistical evaluations were initiated in the 1870 s but serious investigations began in 1891, when Berlin surgeon Ernst Julius Gurlt (1825–1899) started collecting annual reports on the effects of chloroform as an anaesthetic (Gurlt 1891). By the end of the 19th century, Gurlt's statistics included 240,806 cases, which allowed rare side effects to be detected according to the current statistical knowledge (Herkner and Müller 2011). Concurrently discussions on how to minimise the risk of chloroform as an anaesthetic occurred. Experts strongly recommended that chloroform should not be used as an anaesthetic, if the risk of the anaesthesia exceeded that of the patient's illness. Further, chloroform should not be used if the patient could tolerate the pain of the surgical procedure without the chloroform or with other analgesic agents (Schleich 1906). If chloroform needed to be used as the anaesthetic, then it should be administered under the continuous supervision of an experienced physician, and the chloroform concentration in the air should not exceed 4%. Therefore, in the modern sense, this procedure for chloroform use clearly showed signs of a rational benefit-risk evaluation.

2.2. Antipyrine

Phenazone was one of the first synthetic analgesics. It was patented in 1883 and marketed under the trade mark antipyrine soon thereafter (Sneader 2005; Hennig 1993). Initially, antipyrine was considered chemically related to quinine; thus, it was used as an antipyretic. By 1883, Wilhelm Filehne (1844–1927) had successfully tested antipyrine in healthy people and in febrile patients. His tests indicated that antipyrine should be administered at doses of 5–6 g per day, usually within 3 h. Soon thereafter, other physicians began to test antipyrine (for details see Schneider 2014). Several case reports that typically included 10–30 patients were published in the medical literature. Before antipyrine had reached the market, approximately 300 cases were published and this allowed physicians and patients to identify common and very common side effects. However, in the early years, the side effects of antipyrine were not statistically analysed. It was more effective at reducing fevers than the traditional methods of bathing in cool water or applying quinine in fevers that were not malaria-related and it seemed to only have a few side effects that were well-tolerated, such as skin rashes and digestive system complaints. Summaries of the side effects were published in textbooks around 1900 (Lewin 1899; Kebler et al. 1909; Seifert 1915). Almost all of these side effects are mentioned in the current Summary of Product Characteristics for phenazone, which is still marketed today (Table). The textbooks even mentioned more side effects than regarded as relevant today, which can be attributed to the high doses given in the early years or drug impurities no longer common. These refer to diseases of the eye and the nervous system.

In the early years of antipyrine administration, the number of patients that used the drug was not sufficient, according to the statistical analyses, to detect rare and very rare side effects. However, a very severe side effect known as toxic epidermal necrolysis (TEN; or the Lyell or Stevens-Johnson syndrome) was fully described in detail by 1887 (Schneider and Helmstädter 2014). The Jewish physician Baruch Spitz (1854–1932) was undeniably the first person to describe a case of TEN after antipyrine ingestion. A 20-year-old woman was given antipyrine and told to take a daily dose of 1–2 g per day. After one week, the woman developed a measles-like, confluent exanthema accompanied with oedema of the lips and eyelids. Two days later, large blisters developed and the epidermis peeled off the body in large swaths. The patient suffered from severe pain, was unable to open her eyes and her body temperature was moderately elevated. The woman recovered slowly *ad integrum*. Dr. Spitz concluded that antipyrine may have unpredictable and dangerous side effects in certain patients and that these effects could not be anticipated (Spitz 1887). Lewin also refered to this report in his textbook (Lewin 1893), while Stevens and Johnson as well as Lyell described the syndrome not before 1922 (Stevens and Johnson 1922) and 1956 (Lyell 1956), respectively.

In the first seven years of antipyrine use (1883–1890), approximately 40 reports, which described the experiences of more than 1000 patients, were published in the medical literature (for full details see Schneider 2014). The largest study was conducted by Emil Knebel in Wiesbaden during a typhus epidemic. He treated 371 patients and concluded that antipyrine was a useful and safe drug (Knebel 1886).

2.3. Sulfonal

Eugen Baumann (1846–1896) synthesized sulfonal and it was introduced as a sleep-inducing drug in 1888 by Alfred Kast (1856–1903). The hypnotic action was initially detected in animal experiments with dogs. Several physicians tested sulfonal and frequently reported their findings in medical journals. The majority of the physicians stated that

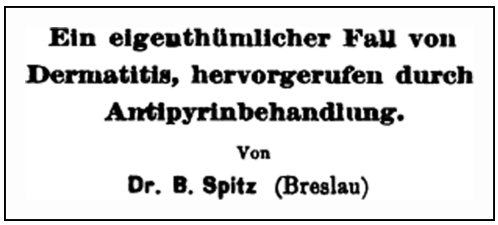
sulfonal had advantages over earlier hypnotics such as morphine, chloral hydrate and bromide salts. Side effects were mild and consisted of a prolonged action, usually known as hang-over. Sulfonal was also used in psychiatric patients, where the prolonged effect was desirable because it kept agitated patients calm for longer periods of time. In the early years of sulfonal administration, the published reports included information about several hundred patients but only some authors tried to summarize their results using statistics. For example, Schwalbe (1888) found that 66% of the patients (n = 50) slept well after treatment, 24% still had trouble sleeping and 10% did not feel that sulfonal worked. A detailed numerical summary was later given by Lewin (1893). Side effects were usually mild until some single fatalities were reported. These fatalities were generally accompanied by dark, discoloured urine, which was soon identified as a symptom of haematoporphyrinuria (Mayer 2010). Discovering this symptom caused physicians to recommend observing a patient's urine during sulfonal therapy as a primary risk reducing method. Maximum daily doses of 2 g for men and 1 g for women were recommended (Kast 1893). In the first seven years after sulfonal entered the marketplace, more than 30 publications appeared in the medical literature, which reported the experiences of several hundred patients (for full details see Schneider 2014) allowing some kind of benefit-risk evaluation.

3. Discussion

In the 19th century, the advent of new chemical entities intended for medicinal use was accompanied by novel challenges pertaining to drug safety. It was the purpose of this study to explore how and how far considerations were made about risks of treatment with substances not related to anything formerly known. That time, industry had not developed an infrastructure for clinical pharmacology investigations and there were no regulatory bodies that limited a drugs entry into the market. Pharmacological actions were generally detected by accident, in experiments of physicians on themselves, or in small animal studies. The drugs were administered to patients rather quickly and large-scale studies in healthy volunteers were not conducted. Each physician determined if and with what circumstances a newly developed drug could be safely administered. The physicians were aware that the novel drugs had side effects and therefore acted with considerable caution. They regularly shared their experiences with colleagues through journal publications and conferences. A literature review shows that in a remarkable short period of time a considerable amount of data was collected, which, however, was not subject to sound statistical evaluation. Attempts were made by the British committees for the evaluation of inhalation anaesthesia methods and the German annual reports by Gurlt in the 1890 s collecting data of more than 200.000 chloroform administrations. The synthetic compounds antipyrine and sulfonal were tested by physicians all over the

Table: Side effects of phenazone reported around 1900 compared to the information given today

ICD-10 classification (2011)	Lewin (1899)	Kebler et al. (1909)	Seifert (1915)	Summary of Product Characteristics 2008
Diseases of the blood and blood forming organs				Alteration in blood formation
Diseases of the digestive system	Feelings of disgust	Digestive tract with abnormal symptoms	Feelings of disgust, abdominalgia, haematemesis,	Nausea and vomiting
Diseases of the skin and the subcutaneous tissue	Rash, pemphigus, heavy stomatitis, blemishes on the buccal and labia mucous membranes, bloated face, gangrene after injection, fever	Urticaria, rash, itching	Skin eruption, erythema, fixed drug eruption, stomatitis, Erythema exsudativum multiforme, measles like rash	Fixed rash, urticaria, inflammation and swelling of the mucosa, Erythema multiforme, E. nodosum, Angioedema, Toxic epidermal necrolysis
Injuries, poisoning and certain consequences due to external causes	Curious excitation, freezing, dyspnoea, collapse	Coldness of the extremities, rapid and feeble pulse, collapse, vertigo	Antipyrine hypersensitivity, abnormal chills, cardiac disorders, vertigo, collapse	Shock symptoms, cold perspiration, dyspnoea, uneasiness in the cardiac region, vertigo, drop in blood pressure
Diseases of the eye and adnexa	Temporary or entire blindness	Temporary or entire blindness	Temporary or entire blindness	
Diseases of the nervous system	Epilepsy, convulsions, salivation, seizures in head, neck, larynx, jittering of the hands and tongue, paralysis	Excessive restlessness or convulsions, salivation	Epileptic seizures, convulsions, salivation	
Mental and behavioural disorders	Apathy, ravings, stupor	Ravings	Apathy, Ravings	


Ein eigenthümlicher Fall von Dermatitis, hervorgerufen durch Antipyrinbehandlung.

Von

Dr. B. Spitz (Breslau)

Fig. 2: Title of Spitz' publication, first report of drug induced TEN (Spitz 1887).

country before the drug had entered the market (i.e. in a multicentre pattern). They received the drug from the manufacturer and typically reported their results immediately after a number of 10-30 patients had been treated. Several hundred cases for antipyrine and sulfonal were reported in the first few years, which in any case allowed the detection of common side effects according to today's statistical knowledge. However, closely following the medical literature was important for the physician to stay up to date. The high doses that were administered in the beginning (i.e. 5–6 g per day for phenazone), certainly helped to identify side effects. In some cases (Rosenbach 1888), a placebo control and a blinded study design were suggested; however, these types of studies were not common. Not necessarily in terms of statistics, also very rare side effects were detected early. A prominent example is drug induced toxic epidermal necrolysis (TEN), commonly known as Stevens-Johnson- or Lyell Syndrome. This reaction has clearly been described by Baruch Spitz (1854–1932) as a side effect of antipyrin in 1887, i.e. several decades before Stevens, Johnson, and Lyell (Schneider and Helmstädter 2014)

Early attitudes towards balancing the benefits and risks of the new compounds were evident. Doses were restricted as part of the risk-reducing recommendations. Side effects were summarized in textbooks, in the late 19th and early 20th centuries (Lewin 1881, 1893, 1899; Kebler et al. 1909; Seifert 1915), which for antipyrine, represents most of side effect knowledge known today. Thus, benefit-risk evaluations clearly existed in the early days of artificial drug compounds. However, in the early years, every physician had greater responsibility than he has today, when, statistically evaluated industrial research and its control by the regulatory bodies provide a much sounder basis for decision making.

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