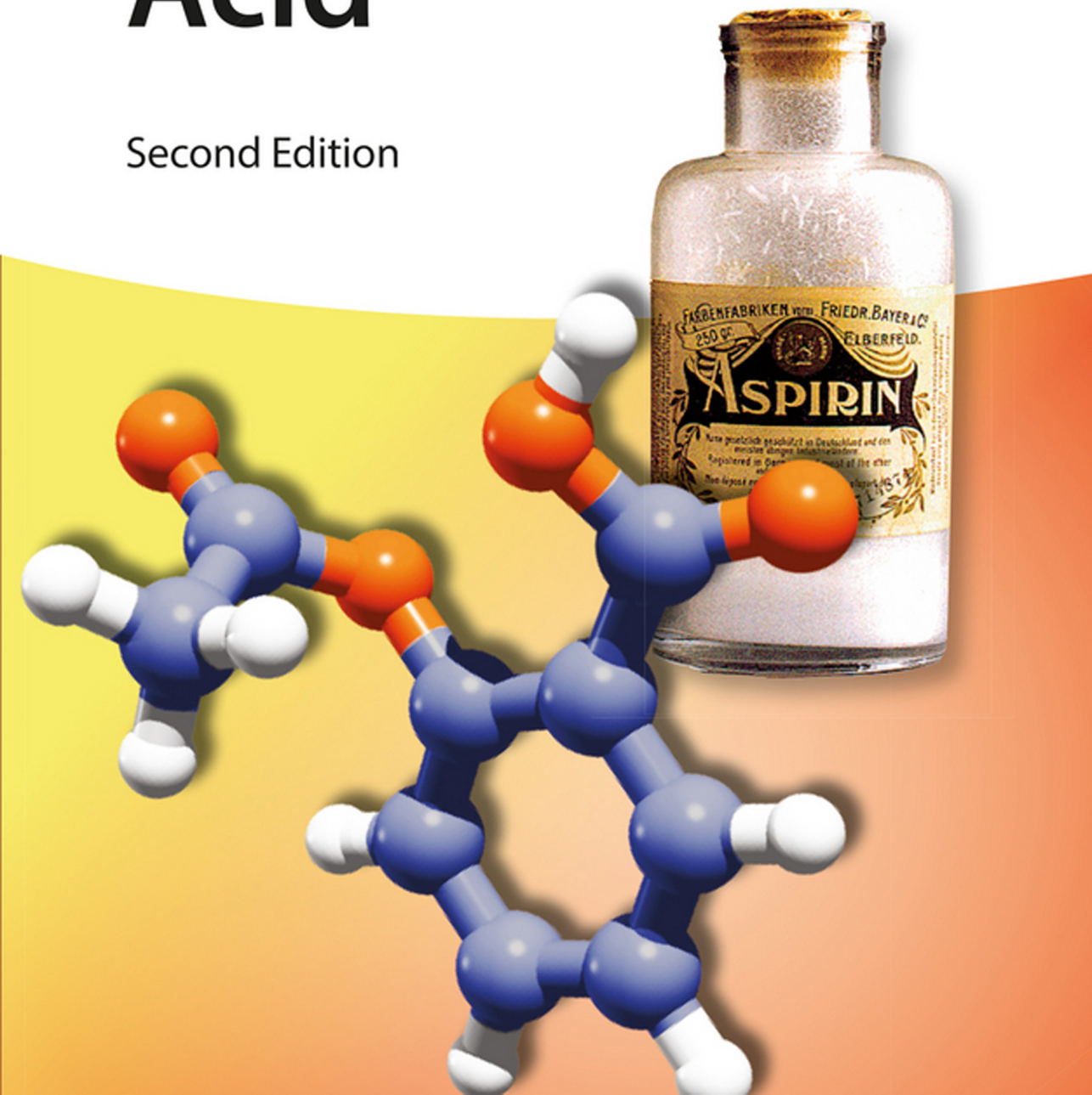
WILEY-VCH

Karsten Schrör

Acetylsalicylic Acid

Second Edition



Karsten Schrör

Acetylsalicylic Acid

Karsten Schrör

Acetylsalicylic Acid

Second Edition

WILEY-VCH
Verlag GmbH & Co. KGaA

Author

Prof. Dr. Karsten Schrör
Institute for Pharmacology and Clinical Pharmacology
University of Düsseldorf
Universitätsstr. 1
40225 Düsseldorf
Germany

Cover
Picture of the bottle with kind permission of Bayer AG.

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

Print ISBN: 978-3-527-33805-4
ePDF ISBN: 978-3-527-68502-8
ePub ISBN: 978-3-527-68504-2
Mobi ISBN: 978-3-527-68503-5
oBook ISBN: 978-3-527-68505-9

Typesetting Thomson Digital, Noida, India

Printed on acid-free paper

Contents

Preface

After the remarkable success of the first edition of this book – a first comprehensive overview of all aspects of pharmacology, toxicology, and clinics of aspirin – both the author and the publisher felt that an updated edition is needed: More than 2500 entries on "aspirin" are found during the last 5 years alone in the publication data base "Pubmed" – every year. Here, a completely revised and actualized edition of the first version is presented, trying to consider all of the relevant information on this remarkable drug until the end of 2015.

A major new finding regarding the pharmacodynamics of aspirin was the detection of numerous hitherto unknown acetylation targets and the increasing awareness that the irreversible and essentially nonselective acetylation process, in case of proteins possibly associated with modifications of their steric structure and function, is the key mechanistic event in the pharmacology of aspirin at doses that are currently used. This is exactly opposite to the original concept at the time of clinical introduction of aspirin in 1899 when the metabolite salicylate was considered to be the active drug and unmetabolized aspirin just an inactive prodrug. The irreversibility of acetylation has also consequences for the duration of aspirin's action. This is determined by the turnover rate of the affected target (protein) rather than by the short half-life of aspirin in the circulation, amounting for only a few minutes.

Interesting news also came from the pharmacokinetics. A new fast-disintegrating aspirin formulation with a more rapid onset of action and about threefold higher peak plasma level was introduced in the market in Germany and some other countries and might replace the standard aspirin tablet in the future.

Significant new patient data have also been generated by the widespread clinical use of the compound. This includes thrombotic diseases such as prevention of arterial and venous thromboembolism and preeclampsia. Another exciting field of clinical research is the possible use of aspirin in chemoprevention of malignant diseases, most notably colorectal cancer. The US-PSTF has just filed a draft to recommend prophylactic aspirin for primary prevention in certain groups of patients at elevated risk. A final recommendation about the use of aspirin in primary prevention will be probably published within the next months. Finally, numerous new clinical trials on aspirin as a single drug or as comedication in several clinical indications have been published since 2010 and are discussed in some detail here.

As in the past, in the making of this new edition, many friends and colleagues worldwide have extended their considerable help and support. I am grateful to all of them. The technical help of Petra Rompel (Düsseldorf) in generating the illustrations is also gratefully acknowledged.

Düsseldorf, March 2016 Karsten Schrör

1 General Aspects

Acetylsalicylic Acid, Second Edition. Karsten Schrör.

1
General Aspects

1.1
History

1.1.1
From Willow Bark to Salicylic Acid

1.1.1.1 Anti-Inflammatory and Analgesic Effects of Willow Bark and Leaves

Medical Effects of Willow Bark Treatment of maladies by plants or extracts thereof is as old as the history of mankind. This is also true for fever and pain, two particularly frequent and inconvenient symptoms of acute illnesses but also typical for osteoarthritis and rheumatism, two examples of chronic painful diseases. Rheumatism was already known in old Egypt as seen from cartilage alterations in Egyptian mummies. The Egyptians were also aware of the pain-relieving effects of potions made from myrtle and willow leaves. Clay tablets from the Sumerian period also contained information about the use of willow leaves as medicines. *Hippocrates* recommended leaves of the willow tree for medical purposes about 400 BC. *Pliny* (compilations) and *Dioscurides* (*Materia Medica*) also recommended decocts of willow leaves or ash from willow bark for treatment of sciatica (lumbago) and gout at about 100 AC. Outside Europe, it were the Nama (Hottentots) in Southern Africa who had "for a long time" used tea made from bark of willow trees for treatment of rheumatic diseases (cited after Ref. [1]). This comment was made by Dr. Ensor from Cape Town (South Africa) in his reply to a publication of Dr. MacLagan in 1876 [2] describing for the first time positive experience with salicylates at 2 g/day for treatment of rheumatism.

The First Published Clinical Trial The first known public communication on the medical use of willow bark extracts in modern times came from Reverend *Edward Stone* [3] from Chipping Norton (Oxfordshire, England). He treated some 50 cases of "aigues, fever, and intermitting disorders" with a redissolved powdered dry bark preparation of willow tree. The doses were about "20 gr(ains) [≈1.3 g] to a dram of water every 4 hours." On June 2, 1763, he wrote a letter to the Earl of Macclesfield, the then President of the Royal Society in London, entitled "An account of the success of the bark of the willow in the cure of aigues." In this letter, he summarized his opinion about this treatment as follows:

> *. . . As this tree delights in moist or wet soil where agues chiefly abound, the general maxim, that many natural maladies carry their cure along with them or that their remedies lie not far from their causes, was so very apposite to this particular case, that I could not help applying it; and this might be the intention of providence here, I must own had some little weight with me . . . .*

After claiming to have obtained good results, he concluded:

Acetylsalicylic Acid, Second Edition. Karsten Schrör.

. . . I have no other motives for publishing this valuable specific than that it may have a fair and full trial in all its variety of circumstances and situations, and that the world may reap the benefits accruing from it.

1.1.1.2 Salicylates as the Active Ingredients of Willow Bark and Other Natural Sources

Detection and Preparation of Salicin from Willow Bark In 1828, the German pharmacist *Johann Andreas Buchner* was the first to prepare a yellowish mash with bitter taste from boiled willow bark, which he named Salicin, after the Latin word for willow *(salix).* He considered salicin as the active antipyretic ingredient of willow bark and recommended its use for treatment of fever. A similar conclusion had earlier been reached by the Italians *Brugnatelli* and *Fontana* in 1826 using a less purified preparation of willow bark. They also considered salicin as the active principal component of willow bark (cited after Ref. [4]). In 1830, the Frenchman Henry *Leroux* was the first to obtain salicin in crystalline form. Only 3 years later, in 1833, the pharmacist *Merck* in Darmstadt (Germany) announced highly purified salicin from willow bark for use as an antipyretic for half of the price of quinine (cited after Ref. [5]) – at that time a really attractive offer.

Salicin from Natural Sources as Starting Material to Make Salicylic Acid Salicin is not only the active antipyretic ingredient of willow bark but also the reason for its strong bitter taste and the irritation of stomach mucosa. Both limited its practical use. Salicin hydrolyzes in aqueous media to glucose and salicylic alcohol (saligenin). Saligenin has no bitter taste and can be easily oxidized to salicylic acid. *Raffaele Piria*, an Italian, was the first to successfully synthesize salicylic acid (acide salicique ou salicylique) from salicin in 1839 and also correctly determined the empirical formula $C_7H_6O_3$. This led to the possibility of replacing the poorly palatable salicin by salicylic acid, for example, as a good water-soluble sodium salt. This became practically relevant after new and abundant natural sources for salicylates were detected. These included wintergreen oil obtained from the American Evergreen (*Gaultheria procumbens*) and spireic acid (acidum salicylicum) from the American teaberry (*Spiraea ulmaria*). Gaultheria oil (wintergreen oil) consists of about 99% of methyl salicylate from which free salicylic acid can easily be obtained. However, production of salicylates by plants is also an important defence mechanism in itself.

*Efficient communication between the pest-colonized and noncolonized plants is vital for timely manifestation of defenses that restrict systemic spread of pests. Airborne signals are involved in these processes. Methyl salicylate is a volatile compound that is made by a number of plants and is suggested to act as a mobile airborne signal in plant defence by activation of systemic acquired resistance. This confers enhanced resistance against a broad spectrum of pathogens (*Section 2.2.2*)* [6].

1.1.1.3 Chemical Synthesis of Salicylic Acid

The Kolbe–Schmitt Synthesis The modern pharmaceutical history of salicylates and its derivatives starts with the chemical synthesis of the compound. In 1859, *Hermann Kolbe*, a German and Professor of Chemistry in Marburg, produced the first fully synthetic salicylic acid from the already known decomposition products phenol and carbonic acid, that is, sodium phenolate and carbon dioxide. Kolbe then stimulated his assistant *Rudolf Wilhelm Schmitt* to further improve the technology, eventually resulting in doubling of the salicylic acid yield. Schmitt also elucidated the reaction kinetics. This base-promoted carboxylation of phenols under high pressure allowing the synthesis of salicylic acid derivatives is known since then as the "Kolbe–Schmitt reaction." *Friedrich von Heyden*, a student of Schmitt, was introduced to Kolbe who encouraged him to develop a procedure to make the compound on an industrial scale. Von Heyden was the first to receive a patent for this procedure. The development of an appropriate technology to synthesize large amounts of

salicylate, independent of the limited availability of natural sources with varying contents and seasonal variations of the active ingredient, opened the door for its broader practical use and thus caused a massive drop in price: The price of 100 g of salicylic acid prepared from salicin from natural sources (gaultheria oil) dropped from 10 to 1 Taler/100 g (Dollar = American for Taler) for the chemical product made through Kolbe's synthesis (cited after Ref. [7]).

Von Heyden started the large-scale production of salicylic acid in the kitchen of his mansion, the "Villa Adolpha" in Dresden (Saxony). In 1874, the site was moved to Radebeul, a suburb west to Dresden, where he founded the factory "Salizylsäurefabrik Dr. von Heyden." This plant was extremely effective: After making 4 tons of salicylic acid in the first year, the annual production was increased to 25 tons only 4 years later and continued to grow steadily. Kolbe and von Heyden received patents for the synthesis of salicylate in many European countries and the United States [8]. Interestingly, after solving some legal issues, von Heyden's plant also produced the salicylic acid that was later used by Bayer to make aspirin [9].

Practical Use of Salicylate After salicylate as a cheap chemical became available on an industrial scale, that is, in essentially unlimited amounts, the compound was tested for new practical applications. For example, salicylic acid was soon found to have antiseptic properties that could be used to preserve milk and meat. The compound was also recommended as an alternative to phenol (carbolic acid), which, was the antiseptic of choice in surgery those days. The antipyretic action of salicylate was for a time also attributed to its antiseptic activity, until it was shown that the sodium salt with little antiseptic properties was an equally effective antipyretic (cited after Ref. [1]). Importantly, salicylic acid was also studied as a potential drug in a large variety of diseases and thus became the first synthetic drug ever developed. In 1875, *Ebstein and Müller* [10] detected the blood sugar-lowering action of the compound. Shortly thereafter, the uricosuric action of salicylate was described. Thus, salicylates appeared to be useful for treatment of diabetes and gout.

Salicylic Acid as an Anti-Inflammatory Antirheumatic Agent Of the several discoveries regarding medical applications of salicylates, the most significant was the finding that synthetic salicylates were potent anti-inflammatory analgesics and extremely useful for treatment of rheumatic diseases. *Franz Stricker* from Berlin was the first to publish that sodium salicylate was not only an antipyretic remedy but also as an effective drug for treatment of rheumatic bone and joint diseases [11]. He was the first to clinically introduce salicylate in 1876 as an analgesic antirheumatic drug at the Charité in Berlin [12]. Two months later, Scottish physician *Thomas J. MacLagan* [13] published the first of a series of articles showing that administration of salicylate to patients with rheumatic fever resulted in the rapid disappearance of fever and pain. Similar results were reported by the Frenchman *Germain Sée* 1 year later [14]. These three studies marked the beginning of the systematic therapeutic use of salicylates as analgesic anti-inflammatory drugs in medicine.

Summary

Extracts or other preparations from willow bark or leaves were used in ancient times as household remedies for the treatment of fever, inflammation, and pain. These ancient uses have been rediscovered only in the eighteenth century: In 1763, the first communication on successful use by Reverend Edward Stone of an aqueous extract of powdered willow bark in the treatment of "aigue and feverish diseases" was published in the United Kingdom.

Search for the active ingredient of willow bark initially resulted in the detection of salicin, from which salicylate as the active fraction could easily be prepared. Further rich natural sources of salicylates were found, among them being the American evergreen (*Gaultheria procumbens)* and spireic acid (acidum salicylicum) from the American teaberry (*S. ulmaria*).

Kolbe was the first to succeed in making fully synthetic salicylate from sodium phenolate and carbon dioxide in 1859, a procedure later improved by Schmitt. Some further improvements on procedure by von Heyden eventually resulted in the foundation of the plant "Salicylsäurefabrik von Heyden" in 1874 that produced salicylic acid in large scale. This new compound was not only accepted for wide practical use but also became the first entirely synthetic drug worldwide; it was introduced in the clinics as an analgesic antirheumatic by Stricker in Berlin 1876.

References

1 Gross, M. and Greenberg, L.A. (1948) *The Salicylates: A Critical Bibliographic Review*, Hillhouse Press, New Haven, CT.

2 MacLagan, T. (1876) The treatment of rheumatism by salicin and salicylic acid. *BMJ*, **1** (803), 627.

3 Stone, E. (1763) An account of the success of the bark of the willow in the cure of agues. *Philos. Trans. R. Soc. Lond.*, **53**, 195–200.

4 Sharp, G. (1915) The history of the salicylic compounds and of salicin. *Pharm. J.*, **94**, 857.

5 Horsch, W. (1979) Die Salicylate. *Pharmazie*, **34** (9), 585–604.

6 Shah, J. (2009) Plants under attack: systemic signals in defence. *Curr. Opin. Plant. Biol.*, **12** (4), 459–464.

7 Bekemeier, H. (1977) On the history of the salicylic acid. *Wiss. Beitr. Martin Luther Univ. Halle Wittenberg*, **42** (R34), 6–13.

8 Reschetilowski, W., Remane, H., and Schuhmann, A. (2012) *Historische Stätten der Chemie: Ehemalige Salicylsäurefabrik und spätere Chemische Fabrik Dr. F. von Heyden Radebeul*, Gesellschaft Deutscher Chemiker.

9 Schreiner, C. (1997) *100 Years of Aspirin. The Future Has Just Begun*, Bayer AG.

10 Ebstein, W. and Müller, J. (1875) Weitere Mittheilungen über die Behandlung des Diabetes mellitus mit Carbolsäure nebst Bemerkungen über die Anwendung von Salicylsäure bei dieser Krankheit. *Berlin Klin. Wochenschr.*, **12**, 53–56.

11 Stricker, S. (1876) Über die Resultate der Behandlung der Polyarthritis rheumatica mit Salicylsäure. *Berlin Klin. Wochenschr.*, **13**, 1–2, 15–16, 99–103.

12 Hangarter, W. (1974) Herkommen, Geschichte, Anwendung und weitere Entwicklung der Salizylsäure, in *Die Salizylsäure und ihre Abkömmlinge* (ed. W. Hangarter), F.K. Schattauer, Stuttgart, pp. 3–11.

13 MacLagan, T. (1876) The treatment of rheumatism by salicin and salicylic acid. *British Med. J.*, **1** (803), 627.

14 Sée, G. (1877) Études sur l'acide salicyliqué et les salicylates; traitement du rhumatisme aigu et chronique, de la goutte, et de diverses affections du système nerveux sensitif par les salicylates. *Bull. Acad. Nat. Med. (Paris)*, **6**, 689–706, 717–754.

1.1.2 Synthesis of Acetylated Salicylic Acid and First Medical Use

1.1.2.1 The Invention of Acetylated Salicylic Acid

Despite the undisputed benefits of sodium salicylate in the treatment of pain, fever, and inflammatory disorders, there were several problems with the practical handling of the compound. These included an unpleasant sweetish taste and, in particular, irritations of the stomach, often associated with nausea and vomiting. Another disturbing side effect was a hearing disorder called tinnitus. These side effects occurred quite frequently at high doses of several grams of salicylate per day, which had to be taken regularly by patients suffering from chronic (rheumatic) pain. Thus, after an effective technology to generate large amounts of entirely synthetic salicylate became available, several efforts were made to improve the pharmacological properties of the compound by appropriate chemical modifications, eventually resulting in increased efficacy as well as improved gastric tolerability when the substance was made more palatable. Acetylation was a favored chemical method at the time to reach this goal. Several researchers addressed this issue by acetylating salicylic acid with different results [1–3] until chemists of the firm of "Farbenfabriken Bayer" in Elberfeld, today part of Wuppertal (Germany), succeeded in synthesizing acetylated salicylic acid from salicylic acid and acetic anhydride in a chemically pure and stable form.

The History of Bayer Aspirin Three persons at Bayer were intimately involved in this development. All three were chemists and all of them were of the same age group – born in the 1960s, when the knowledge in organic chemistry had just started to explode. The first to be named was *Carl Duisberg* (Figure 1.1.2-1). After completing his dissertation in Jena with a study on acetoacetate esters (!), he decided to pursue his career in the chemical industry. In 1883 he joined the Bayer company and became head of the research only 5 years later [4]. *Arthur Eichengrün* (Figure 1.1.2-1) joined the Bayer Company in 1895 and became head of the Pharmaceutical Research Department that was newly founded by Duisberg [5]. According to a report, written by Eichengrün 50 years later [6], it was his idea to acetylate salicylate in order to make it more palatable and also avoid the unpleasant irritation of the stomach. As mentioned above, the concept of acetylation of drugs to improve their efficacy was not new at the time. It had already been successfully used in making phenacetin, a powerful analgesic, by the Bayer Company. Phenacetin was synthesized via acetaminophen from *p*-nitrophenol, a waste product of Bayer's dye fabrication [4]. This positive experience probably stimulated the company to make a more widespread application of acetylation procedures to other chemicals and drugs. This included guaiacol, cinchonine, morphine – and salicylic acid. *Felix Hoffmann* (Figure 1.1.2-1) was the chemist

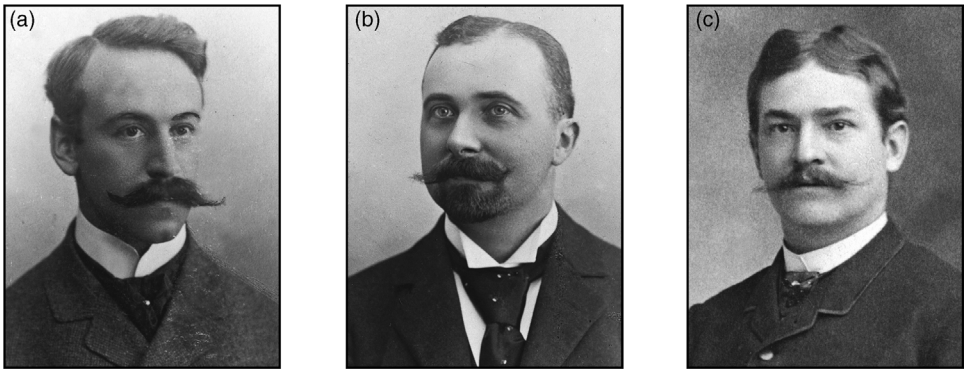


Figure 1.1.2-1 (a) Arthur Eichengrün (1867–1949). (b) Felix Hoffmann (1868–1946). (c) Carl Duisberg (1861–1935). (With kind permission from Bayer.)

working on this issue "on Eichengrün's advice" [6]. He was the first person to develop a technology to produce chemically pure and stable acetylsalicylic acid from salicylic acid and acetic anhydride. According to a handwritten note in his laboratory diary, this success was achieved on August 10, 1897, (Figure 1.1.2-2). Later he wrote:

> *. . . When salicylic acid (100.0 parts) is heated with acetic anhydride (150.0 parts) for 3 hours under reflux, the salicylic acid is quantitatively acetylated . . . . By its physical properties, e.g. its sour taste without being corrosive, the acetylsalicylic acid differs favorably from salicylic acid, and is now being tested in this respect for its usefulness*

Another person at Bayer should also be mentioned in this context: *Heinrich Dreser*, the then head of the Department of Pharmacology. Dreser was not interested in this kind of research and initially did not believe in any clinically useful properties of the new compound ("the compound is of no value"). However, in his later description of the pharmacology of aspirin, he acknowledged the better taste and less gastric irritation [7]. Initially, he was also not informed by the pharmacists about its successful clinical testing, although according to his contract with the company, the pharmacists should have had reported this finding to him before undertaking further activities [2]. Thus, he was probably not amused to learn that without his knowledge and against his declared intention, the new compound was – even successfully – tested in patients. According to Eichengrün and other sources, he did everything to block the further development of aspirin, while Duisberg emphatically supported the activities of Eichengrün and Hoffmann and, as expected, finally succeeded. The further development and clinical introduction of acetylated salicylate as an antipyretic analgesic, eventually resulting in the worldwide spread of the compound, is his merit.

The new drug received the trade name "aspirin," which is composed from "*a*cetic" and "*spir*eic acid," a former name of *o*-hydroxybenzoic acid (salicylic acid), originally prepared from *S. ulmaria*, one of the richest natural sources of salicylates.

The first description of the pharmacology of aspirin was published in 1899 by Dreser. The names of the two chemists Hoffmann and Eichengrün were not mentioned in this paper. Dreser considered aspirin as a better tolerable prodrug of the active metabolite salicylic acid with the positive pharmacodynamic property not to be cardiotoxic [7]. According to Eichengrün [6], Dreser had nothing to do with the invention. However, it was Dreser who took the financial benefits from the discovery, not Eichengrün and Hoffmann [8]. According to a contract with Bayer, the products invented under the direction of Eichengrün had to be patented in Germany to get a royalty for the inventor from the company [6]. Acetylsalicylic acid was registered on February 1, 1899 under the trade name "Aspirin®" by the Imperial Patent Bureau (Kaiserliches Patentamt) in Berlin and a few weeks later introduced to the market. This was the first time that a drug was dispensed as a product (powder or tablet) made by chemists according to quality standards of their company and not dispensed as a product manufactured as a powder by a pharmacist. This caused long-lasting and intense discussions about the role of pharmacists as the primary controller of drug production [9].

"Aspirin" did not receive recognition as a drug to be patented in Germany or any other European country, except the United Kingdom, where Bayer held a patent until 1905. This patent was declared futile by a British Court in 1905 after a legal action of von Heyden company, the provider of salicylic acid for Bayer. Von Heyden also produced and sold acetylated salicylic acid, but under its chemical name "acetylsalicylic acid" [8].

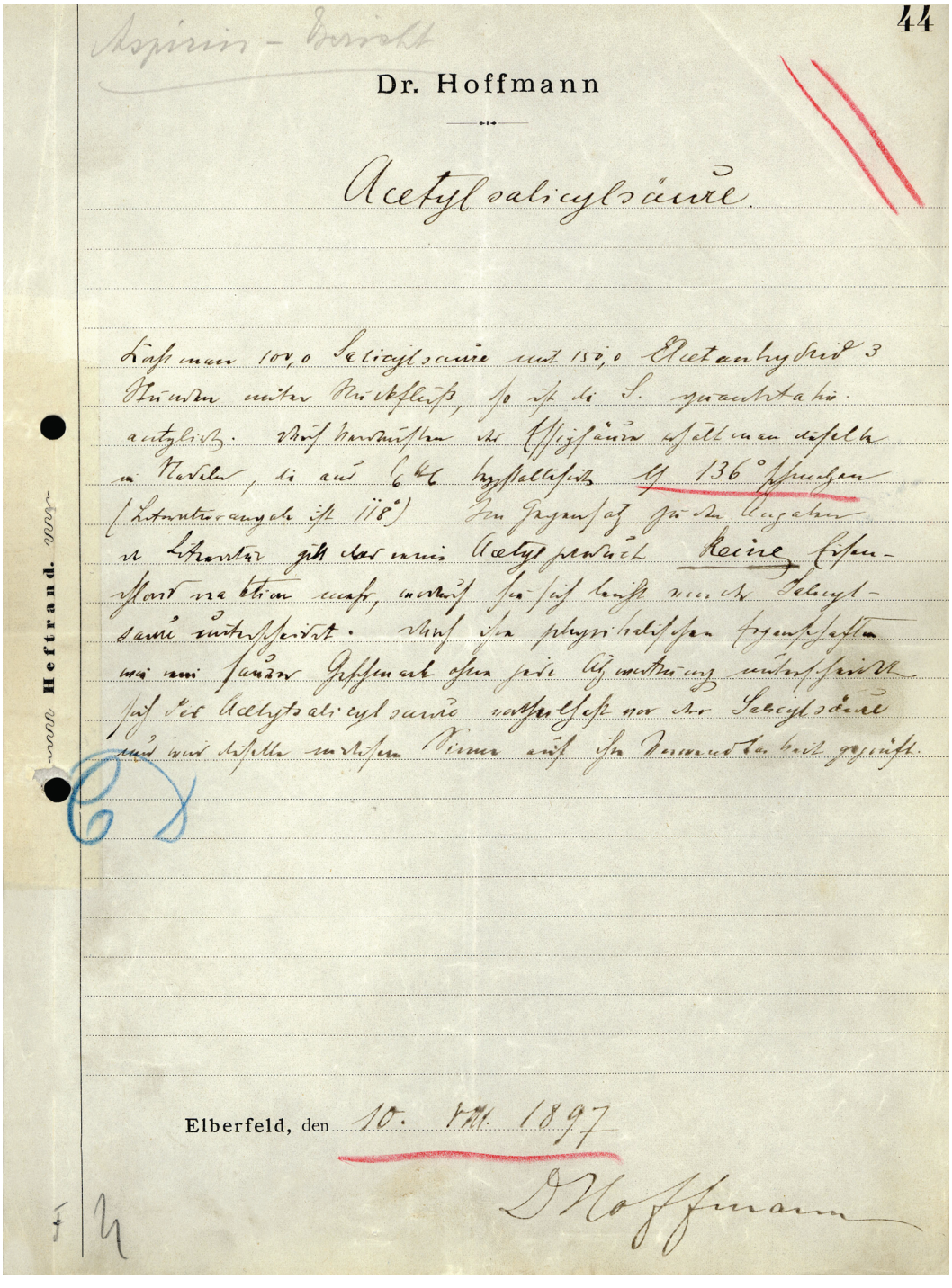


Figure 1.1.2-2 Laboratory record of Dr. Felix Hoffmann from August 10, 1897 containing the first description of successful synthesis of acetylsalicylic acid. (With kind permission from Bayer.)

Bayer marketed the new compound under the Bayer-owned trade name "Aspirin." In the labeling, the product was identified as "monoacetic acid ester of salicylic acid" and advertised as a better tasting replacement for salicylic acid. The aspirin packages did not indicate that aspirin was pure acetylsalicylic acid. Bayer took every effort to keep this trade name as sole property of Bayer. The (numerous) copycats had to use other labeling, mostly they preferred the chemical term "acetylsalicylic acid" while Bayer advertised aspirin as "best replacement for salicylic acid." Doctors (probably) never learned from Bayer's advertising that aspirin was solely a trade name and found it easier to prescribe "Aspirin(um)" [sic!] than "acetylsalicylic acid" [8].

Aspirin was patented 1900 exclusively in the United States (Figure 1.1.2-3).

As a consequence of World War I, in 1917, all patents and trade names of German firms were held enemy property in the United States and, thus, were confiscated [9]. German firms were also no longer allowed to sell their products in the United States [8]. The Bayer assets were auctioned by the US Alien Property Custodian and sold the same year for $5.3 millions to Sterling Drugs, Inc. of New York [10,11]. This company then produced "genuine Bayer Aspirin" for the US market (Section 3.1.1) [12]: It was only in 1994 that the German Bayer AG could buy back the rights of the trademark and the Bayer Cross in the United States (for details, see Ref. [8]).

According to a publication by Sneader and some followers, not Hoffmann but rather Eichengrün should be considered as the true inventor of aspirin [13]. As Eichengrün was Jewish, he could not enjoy the fruits of his remarkable scientific research, including also the invention of several other products in addition to aspirin, such as acetate silk, because of the political reasons during the Nazi regime. Eichengrün was interned in 1944 in a concentration camp and remained there until the end of World War II. Eichengrün in the year of his death (1949) stated in an article, published in the German Scientific Journal *Die Pharmazie*, that it was he and Felix Hoffmann who should be considered as the inventors of aspirin [6].

According to Eichengrün [6], it was Hoffmann who had first worked out the acetylation technology (. . . "welcher [Hoffmann] die Acetylierung ausgearbeitet hatte" . . .), eventually resulting in the synthesis of pure and chemically stable acetylated salicylic acid [14], although, again according to Eichengrün, he did so following "my advices" ("er führte meine [chemischen] Anordnungen aus"). However, the sole, unopposed mention of Hoffmann's name on the US patent application form of 1900 (Figure 1.1.2-3) clearly would not have been possible without the knowledge or even against the will of his two supervisor chemists, Eichengrün and Duisberg. This clearly suggests that both considered Hoffmann's activities in this research as very fundamental, justifying his name as the inventor of aspirin. Because of the complexity of the issue, as already discussed, one should, however, also pay tribute to the significant contributions of Eichengrün and Duisberg in the research and development of aspirin. This will not reduce the outstanding contribution of Hoffmann in this discovery.

Further Attempts to Make Acetylsalicylic Acid At this point, it should be noted that Hoffmann was not the first person who tried to chemically synthesize acetylated salicylic acid. In 1853, *Charles Frédéric Gerhardt*, a Frenchman, from Straßburg (Alsace) described the synthesis of a new compound from acetyl chloride and sodium salicylate, which he named "salicylate acétique" [15].

This publication of Gerhardt was taken by several authors as evidence to ascribe the invention of acetylsalicylic acid to him (e.g., Refs. [3,10,16]. *This is not correct for several reasons. The "acetylsalicylic acid" of Gerhardt, if it was formed at all, solely might have existed as a labile, intermediate raw product of the reaction between acetyl chloride (prepared by him by a suboptimal procedure) and sodium salicylate* [2]. *The chemical structure of "salicylate acétique" was not determined. The physicochemical properties were not those of acetylsalicylic acid but rather those of salicylic acid* [17,18]. *The technical procedure was suboptimal and resulted in simultaneous formation of large amounts of acetic acid anhydride together with acetosalicylic acid anhydride because of an inappropriate processing of the raw product. As a stable end product, Gerhardt only obtained salicylic acid* [19]. *From his experiments, he concluded that acetylated salicylic acid is unstable and in water immediately breaks down to salicylic acid and acetate* [15]. *Both statements are wrong and do not qualify Gerhardt for the claim to have invented the synthesis of acetylsalicylic acid.*

UNITED STATES PATENT OFFICE.

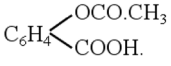
FELIX HOFFMANN OF ELBERFELD GERMANY ASSIGNOR TO THE FARBEN-FABRIKEN OF ELBERFELD COMPANY OF NEW YORK.

ACETYL SALICYLIC ACID.

SPECIFICATION forming part of Letters Patent No. 644,077, dated February 27, 1900.
Application filed August 1, 1898 Serial No. 087,385 (Specimens.)

To all whom it may concern:
Be it known that I, FELIX HOFFMANN, doctor of philosophy, chemist, (assignor to the FARBENFABRIKEN OF ELBERFELD COMPANY, of New York) residing at Elberfeld, Germany, have invented a new and useful Improvement in the Manufacture or Production of Acetyl Salicylic Acid; and I hereby declare the following to be a clear and exact description of my invention.

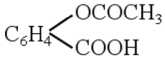
In the *Annalen der Chemie und Pharmacie,* Vol. 150, pages 11 and 12, Kraut has described that he obtained by the action of acetyl chlorid on salicylic acid a body which he thought to be acetyl salicylic acid. I have now found that on heating salicylic acid with acetic anhydride a body is obtained the properties of which are perfectly different from those of the body described by Kraut. According to my researches the body obtained by means of my new process is undoubtedly the real acetyl salicylic acid



Therefore the compound described by Kraut cannot be the real acetyl salicylic acid but is another compound. In the following I point out specifically the principal differences between my new compound and the body described by Kraut.

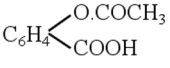
If the Kraut product is boiled even for a long while with water, (according to Kraut's statement,) acetic acid is not produced, while my new body when boiled with water is readily split up, acetic and salicylic acid being produced. The watery solution of the Kraut body shows the same behavior on the addition of a small quantity of ferric chlorid as a watery solution of salicylic acid when mixed with a small quantity of ferric chlorid—that is to say, it assumes a violet color. On the contrary, a watery solution of my new body when mixed with ferric chlorid does not assume a violet color. If a melted test portion of the Kraut body is allowed to cool it begins to solidify (according to Kraut's statement) at from 118° to 118.5° centigrade while a melted test portion of my product solidifies at about 70° centigrade. The melting-points of the two compounds cannot be compared because Kraut does not give the melting-point of his compound. It follows from those details that the two compounds are absolutely different.

In producing my new compound I can proceed as follows, (without limiting myself to the particulars given:) A mixture prepared from fifty parts of salicylic acid and seventy-five parts of acetic anhydride is heated for about two hours at about 150° centigrade in a vessel provided with a reflex condenser. Thus a clear liquid is obtained, from which on cooling a crystalline mass is separated, which is the acetyl salicylic acid. It is freed from the acetic anhydride by pressing and then recrystallized from dry chloroform. The acid is thus obtained in the shape of glittering white needles melting at about 135°centigrade, which are easily soluble in benzene, alcohol, glacial acetic acid, and chloroform, but difficultly soluble in cold water. It has the formula



and exhibits therapeutical properties.
Having now described my invention and in what manner the same is to be performed, what I claim as new, and desire to secure by Letters Patent, is—

As a new article of manufacture the acetyl salicylic acid having the formula:



being when crystallized from dry chloroform in the shape of white glittering needles, easily soluble in benzene, alcohol and glacial acetic acid, difficultly soluble in cold water being split by hot water into acetic acid and salicylic acid, melting at about 135° centigrade substantially as herein before described.

In testimony whereof I have signed my name in the presence of two subscribing witnesses.

FELIX HOFFMANN.

Witnesses:
R. E. JAHN,
OTTO KÖNIG.

Figure 1.1.2-3 The US acetylsalicylic acid patent from February 27, 1900. (With kind permission from Bayer HealthCare.)

In 1859, *Hugo von Gilm*, a pharmacist from Innsbruck (Austria), reported on the synthesis of acetylsalicylic acid [20] as did *Karl Kraut* and his group from Hannover (Prussia) 10 years later [17]. Kraut and his coworkers Schröder and Prinzhorn were also the first to assign the correct structure with the acetyl moiety connected to the phenolic oxygen to the compound. However, these preparations were still impure and contained significant amounts of salicylic acid, as seen from the positive red "Gerhardt-reaction" of salicylate with ferric chloride (Section 2.1.1). In addition, it exhibited physicochemical properties different from acetylsalicylic acid [19,23] (see also comments of Hoffmann in his patent application) (Figure 1.1.2-3). Nevertheless, it was the publication of Kraut that was the reason for decline of patent protection of the Hoffmann synthesis by the German Patent Authorities [21].

Acetylsalicylic Acid: Organic Chemistry versus Pharmacology In contrast to the natural product salicylic acid, *acetyl*salicylic acid could be made only by organic chemistry – although Karl Kraut started his experiments for its synthesis with gaultheria oil as a natural salicylate (salicin) source. During the following 30 years, there were no further attempts to improve the synthetic procedure, although significant progress was made in organic and pharmaceutical chemistry at this time. According to an organic chemist, acetylsalicylic acid was of no particular interest, but solely made to confirm the feasibility of its synthesis. There were also no ideas or concepts about any possible practical application, including its use as a therapeutic. Thus, acetylated salicylic acid probably would have suffered the fate of several hundreds of chemicals before and many thousands thereafter – a product of chemical synthesis, principally easy to make but more difficult in pure and chemically stable form and without any practical value.

Hoffmann and Eichengrün, in contrast, have had combined the available medical knowledge about curative properties of a product from nature with the contemporary organic chemistry with a clear intention to make a new and better therapeutic out of it. These studies would not have been possible without the substantial and continuous support of Carl Duisberg, the then Head of Bayer research. Duisberg later became Chief Executive and Director General at Bayer. His numerous and outstanding efforts inside and outside the Bayer company gained considerable and consistent recognition, in both Germany and abroad [4]. In an obituary in 1935, the London *Times* noted: . . . "his country loses a man who, all things considered, . . . may be regarded as the greatest industrialist the world has yet had . . . ." Therefore, the company had good reason to duly celebrate the 100th anniversary of "his" compound that in the meantime had become the most popular drug in the world [13].

In the context of priorities in science, an interesting comparison between the discovery of aspirin and the discovery of prostacyclin can be made – both also tightly connected with the name of John Vane. Its chemical structure as well as a suggested (later confirmed) enzymatic synthetic pathway was originally described in 1971 by Pace-Asciak & Wolfe. These authors considered the (labile) product as just another prostaglandin – in addition to the dozens of already known compounds. The authors assumed that it was possibly overlooked by earlier investigators because of its low biological activity, tested at the time in bioassay experiments using the rat stomach strip. It also remained uncertain whether the compound was synthesized at all in the intact stomach wall and, if so, was released in biologically active amounts [22].

A completely different approach was followed by the group of John Vane. Their work on prostacyclin started with the discovery of a biological effect – inhibition of platelet aggregation – by an enzymatic product made from prostaglandin endoperoxides by artery walls [23]. *This prostaglandin, originally named as PGX, differed in its biological property from all other known prostaglandins. PGX was later identified as the already known enzymatic product of prostaglandin endoperoxides, described by Pace-Asciak & Wolfe, and was renamed prostacyclin (PGI_2).*

Despite the originality and merits of Pace-Asciak & Wolfe regarding the detection and original description of biosynthetic pathways of natural prostacyclin and its suggested chemical structure, the medical history of