

## Short Article

# One Hundred Years of Aspirin

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Acetylsalicylic acid was synthesized by Gerhardt in 1853 and even put on the market during the 1880s by the firm Merck.<sup>1</sup> Yet the proper history of this medicine begins only in 1897, now more than a hundred years ago, when this miracle amongst medicines was again synthesized at the dyestuffs factory of Friedrich Bayer and the chemical factory of Friedrich von Heyden. About eighteen months later at Bayer they provided this chemical substance with a brand name: Aspirin. The story of the development of Aspirin at Bayer is well known and has been told over and over again.

Felix Hoffmann was painstakingly looking for a substitute for salicylic acid because his father, who suffered from rheumatism, hated taking this medicine. Hoffmann succeeded in his endeavour after actively searching for some time: on 10 August 1897 he synthesized acetylsalicylic acid. The next step was the pharmaceutical trial of this remedy. Bayer's pharmacist, Heinrich Dreser, took care of this, and after tests on animals and himself he discovered the excellent sedative and anti-febrile properties of this substance. On 23 January 1899 they decided to give this substance the brand name of Aspirin and finally, on 6 March 1899, this was registered at the Kaiserlichen Patentsamt Berlin. The dyestuffs factory was able to put acetylsalicylic acid on the market as an over-the-counter analgesic and remedy for rheumatism.<sup>2</sup>

However, was the discovery of this medicine really the result of the actions of the two people mentioned above? A letter from the chemist Arthur Eichengrün (sent from the concentration camp Theresienstadt) throws a different light on the question. Was this discovery not in reality much more the result of teamwork, of trial and error and of intrigues? Later publications and research in the archives of Bayer sustain Eichengrün's opinion.

In this "historical note" the accepted story of the discovery of Aspirin will be confronted with the material available from Bayer's archives on the one hand and some later published historical documents on the other.

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<sup>1</sup> W D Müller-Jahncke and C Friedrich, *Geschichte der Arzneimitteltherapie*, Stuttgart, Deutscher Apotheker, 1996, p. 143; D van Os, *De strijd in de natuur en het geneesmiddel, Inaugurale rede 15 september 1947*, Groningen, Batavia, J B Wolters, 1947, p. 7.

<sup>2</sup> Many brochures produced by Bayer appeared with similar texts. For example: *Aspirin ein Jahrhundertfarmakon*, Leverkusen, Bayer AG, 1983, pp. 24–30; 'De vele levens van een honderdjarige', *EOS Magazine*, Bayer B.V. Mijdecht; and *100 Jahre Acetylsalicylsäure*, Leverkusen, Bayer AG, 1997.

### Bayer's Archives

Originally Bayer was a producer of dyestuffs. Only at the end of the nineteenth century did the company start the production of medicines. The first ones taken into production were the analgesic Phenacetin and the sleeping pill Sulfonal. No research on medicines was carried out then. Discoveries were bought from inventors; Bayer was concerned only with production and marketing. The checking of the production was done in a so-called "Betriebslabor", in a space very near the one where the medicines were produced. Such laboratories were completely unsuited to medicinal research.<sup>3</sup>

Carl Duisberg, chemist and research manager at Bayer, described the situation: "Because our laboratories are totally unsuitable, it is clear we need more chemists to do our scientific research". Something had to change and Duisberg proposed to the management that they should pull down the old laboratories and replace them with a new one.<sup>4</sup> After some hesitation the management agreed, and in 1891 Bayer obtained a, for that time, very modern, large laboratory. In 1896, there were five chemists in Room II, mostly working in the pharmaceutical field.<sup>5</sup> This development created the circumstances needed for chemical and pharmaceutical research. Therefore, as Friedrich Fischer wrote in a commemorative volume, from 1893 on, efforts were made to synthesize new medicines.<sup>6</sup> Similarly, the laboratory journal of Felix Hoffmann, in which he described the synthesis of new molecules, started in 1894.<sup>7</sup>

Unfortunately, in practice the chemists were mostly occupied with research on new production methods for already established medicines, a continuously changing field.<sup>8</sup> Again it was Duisberg who wanted to change this situation and create the circumstances within which there was actually talk of new medicines. When in 1896 he was negotiating the purchase of a new medicine—Protargol, an invention of Eichengrün—he asked him to take up a job at the dyestuffs factory and set up a scientific laboratory.<sup>9</sup> Eichengrün accepted this offer. His task was "to occupy himself, in close collaboration with the science of pharmaceutical chemistry on the one hand and the science of therapeutic medicine on the other, with the synthesis of new physiologically active preparations".<sup>10</sup> He explained the motives for his decision as follows: "A new vision within scientific research and the success of new medicines for other manufacturers . . . made it almost a must for the dyestuffs factory to have a scientific-pharmaceutical laboratory at their disposal".<sup>11</sup> Duisberg had high expectations of Eichengrün, writing to Friederich Bayer jr on Eichengrün's first working day: "Today (October 1, 1896) Dr. Eichengrün started to

<sup>3</sup> Bayer-Archiv. F Fischer, 'Pharmazeutische Laboratorien', in *Geschichte & Entwicklung der Farnefabriken vorm. Friedr. Bayer & Co. Elberfeld in den ersten 50 Jahren*, Leverkusen, Bayer, 1918, p. 436.

<sup>4</sup> Bayer-Archiv. C Duisberg, 'Selbsterlebtes und Schlussbetrachtungen', in *ibid.*, pp. 624–6.

<sup>5</sup> Bayer-Archiv. 'Gründung des Chemisch-Wissenschaftlichen Laboratoriums der Pharma', p. 24, in G Benz, R Hahn, C Reinhardt (eds), *100 Jahre Chemisch-Wissenschaftliches Laboratorium der Bayer AG in Wuppertal-Elberfeld*, Leverkusen, Bayer, 1996.

<sup>6</sup> Bayer-Archiv. Fischer, *op. cit.*, note 3 above, p. 436.

<sup>7</sup> Bayer-Archiv. Pharmazeutisch-wissenschaftliches Labor Elberfeld. Laborberichte, Monatsberichte. Henecka-Jostes. 103/17 E.2a.

<sup>8</sup> Duisberg, *op. cit.*, note 4 above.

<sup>9</sup> Bayer-Archiv. A Eichengrün, 'Pharmazeutisch-Wissenschaftliche Abteilung', in *op. cit.*, note 3 above, p. 411.

<sup>10</sup> Bayer-Archiv, 103/17.E.2.a. Eichengrün: 'Pharmazeutisch wissenschaftliche Abteilung', undated c.1901.

<sup>11</sup> Duisberg, *op. cit.*, note 4 above.

work for us. We hope he will be able to solve a lot of problems for us".<sup>12</sup> From Eichengrün's notes we can conclude that in 1896 there was not yet talk of a scientific laboratory, but under his leadership in December 1899 the pharmaceutical laboratory was divided into a technical and a scientific part, the pharmaceutical-scientific laboratory.<sup>13</sup> Felix Hoffmann, who succeeded Eichengrün in 1908, looked back at the activities of this laboratory:<sup>14</sup> "On an average 500-600 new chemical substances left our department every year . . .". During the years 1897-1914 these yielded 38 new medicines for Bayer. One of these substances was Aspirin.

From 1897 onward, the chemists who were active in pharmaceutical research worked together in Room III of the new laboratory.<sup>15</sup> These chemists had a number of objectives; later on, Eichengrün regularly discussed these with the management.<sup>16</sup> They examined newly invented chemical reactions, alternatives to already patented medicines and improvements to existing medicines.<sup>17</sup> The lab journals of various chemists illustrate this procedure.<sup>18</sup> Georg Meyer-Thurow later described the research organization as it developed at Bayer:<sup>19</sup> "Research was integrated with a strongly developed complex of communication and supervision, motivations and checks". The meeting of the Pharmaceutical Division, which from 1897 was held weekly, and the lab journals are examples of this communication network within Bayer's research department.<sup>20</sup>

What happened in Bayer's pharmaceutical laboratory in 1897, the year in which Aspirin was invented? Hoffmann and Eichengrün were busy researching new derivatives of salicylic acid, as their lab journals illustrate.<sup>21</sup> Hoffmann was the lucky one and on 10 August 1897 he synthesized acetylsalicylic acid.<sup>22</sup> In view of Bayer's structure and Eichengrün's position and instructions, he must have been well informed about the subject on which his colleague Hoffmann was busy. A private document from 1910 mentions only Hoffmann's participation in the invention of Aspirin.<sup>23</sup> Soon after the synthesis of acetylsalicylic acid the pharmacological research was begun. Fritz Hoffmann described how this research was often speedily performed once the chemical examination had been carried out: "Quite often, an inventor had great expectations in the morning, but by the afternoon an angry pharmacist would pronounce a crushing judgement on the rejected product".<sup>24</sup> This quotation not only illustrates the disappointment of the chemist, but also the rapidity with which the chemical synthesis was followed by the pharmacological examination. Therefore it is very strange that Aspirin stayed on the shelf of products

<sup>12</sup> Op. cit., note 5 above, p. 25.

<sup>13</sup> Ibid.

<sup>14</sup> Ibid., p. 27.

<sup>15</sup> Ibid., p. 25.

<sup>16</sup> W Wimmer, *Wir haben fast immer etwas Neues. Gesundheitswesen und Innovationen der Pharmaindustrie in Deutschland, 1880-1935*, Berlin, Duncker & Humblot, 1994, pp. 123-33.

<sup>17</sup> Eichengrün, op. cit., note 9 above, p. 412.

<sup>18</sup> Bayer-Archiv. Pharmazeutisch-wissenschaftliches Labor Elberfeld. Laborberichte, Monatsberichte. Henecka-Jostes. 103/17 .E.2a; Dr Hoffmann, 1-85.

<sup>19</sup> Georg Meyer-Thurow, 'The industrialization of invention: a case study from the German chemical

industry', *Isis*, 1982, 73 (268): 373.

<sup>20</sup> Some protocols of the "Konferenz der pharmaceutischen Abteilung" are in Bayer-Archiv, 169/3.

<sup>21</sup> Bayer-Archiv. Pharmazeutisch-wissenschaftliches Labor Elberfeld. Laborberichte, Monatsberichte. Henecka-Jostes. 103/17 .E.2a; Dr Hoffmann, 1-85. Laborberichte Deichsel-Grüttefien; 103/17.E.2a; Dr Eichengrün: pp. 18, 19, 20 (2 September 1897, 12 October 1897).

<sup>22</sup> Ibid., Dr Hoffmann, 44, 10.VII.1897.

<sup>23</sup> Bayer-Archiv. A Wingler, Betr. Erfindung Aspirin. Leverkusen-Bayerwerk 25.8.1959, p. 5.

<sup>24</sup> Op. cit., note 5 above, p. 25.

## One Hundred Years of Aspirin

rejected by the pharmacist for over a year. What was the reason for this? Alas, research in Bayer's archives does not give us a satisfactory explanation: "After having initially rejected acetylsalicylic acid because of supposed side-effects on the heart, Dreser wrote his study in 1899" concerning the pharmacological aspects of acetylsalicylic acid.<sup>25</sup> This blind spot in the history of the appearance of Aspirin vanished in November 1898 when during a Pharmaceutical Division meeting Duisberg asked for information about the progress of this new medicine: "Dr Duisberg wants to know about the situation concerning acetylsalicylic acid as a replacement for salicylic acid".<sup>26</sup>

When next the production and conservation of this new medicine came up for discussion, both Dreser and Eichengrün, present at the meeting, held their tongues. Two months later, on 23 January 1899, a circular on the name of a new pharmaceutical product was published in which the name "Aspirin" was decided upon.<sup>27</sup> The following events happened in rapid succession. In the same year, on 6 March, the name Aspirin was registered as a brand name and the marketing of this new medicine was discussed at a Pharmaceutical Division meeting.<sup>28</sup> Furthermore, in 1899 the first clinical examinations of C Witthauer and J Wolgemuth came out and Dreser's brochure *Pharmakologisches über Aspirin* was published.<sup>29</sup>

It is very interesting to note that this pharmacological brochure not only appeared after the clinical publications of Witthauer and Wolgemuth, but that also, alongside its almost exclusively physical data, these publications were used to support the drug's clinical effectiveness.

The marketing could start.

### Later Publications

Even after the introduction of Aspirin the historical interest in this remedy continued, as did the regular appearance of publications about the history of its creation. Did they throw more light on the history of this remedy? Most confirm the role of the two heroes, Hoffmann and Dreser, in the invention of this popular painkiller, but sometimes other views emerged. In 1959 a summary of that literature by Dr A Wingle appeared, in which Eichengrün's involvement in the invention of Aspirin is mentioned.<sup>30</sup> The first article to describe Eichengrün as the inventor of Aspirin appeared in the *Daily Mail* of 1 December 1910. Eichengrün himself did not mention his participation in the discovery of this remedy, because in his lecture on twenty-five years of drug synthesis for the German Chemical Association in 1912 he considered only the role of the family general

<sup>25</sup> *Ibid.*, p. 30.

<sup>26</sup> Bayer-Archiv, 169/3. Pharmaceutische Konferenz vom 29 und 30 November 1898, p. 23.

<sup>27</sup> Bayer-Archiv. Aspirin. Cirkular betreffend Benennung eines neuen pharmazeutischen Products, 23 January 1899.

<sup>28</sup> Bayer-Archiv. Pharmaz. Konferenzen 1897–1949 (169/3). Pharmaceutische Abteilung Konferenz 1899.

<sup>29</sup> Examples of clinical examinations which were published shortly after the introduction of Aspirin are: Bayer-Archiv. F Valentin, 'Klinische

Erfahrungen über die Wirkung des Aspirin', offprint from *Deutschen Aerzte-Zeitung*, 15 October 1900, Heft 20: 1–4; E Roelig, 'Ueber Aspirin, ein neues Antirheumaticum', special issue of *Deutschen medicinischen Wochenschrift*, 1900, no. 5: 1–7. For Dreser's brochure see Bayer-Archiv 166/8. Producte A-Z, Aspirin. H Dreser, *Pharmakologisches über Aspirin (Acetylsalicylsäure)*, Archiv für die Geschichte der Physiologie, vol. 76, Bonn, Emil Strauss, 1899, pp. 305–18.

<sup>30</sup> Bayer-Archiv. A Wingle, Betr. Erfindung Aspirin, Leverkusen-Bayerwerk 25.8.1959, pp. 1–7.

practitioner in connection with the remedy's popularity.<sup>31</sup> In later years also, neither Duisberg nor Hoffmann mentioned Eichengrün's involvement.

After, or more precisely during, the second world war, the discussion on the history of the development of Aspirin was stimulated by a letter Eichengrün sent from the concentration camp Theresienstadt.<sup>32</sup> In 1949 this letter was revised for an article in *Pharmazie*.<sup>33</sup> In both instances he described his employment as the new manager of the newly established chemical-pharmaceutical research laboratory of Bayer immediately after the laboratory was built. He was to supervise a number of chemists and, together with them, he performed the necessary examinations of drugs. His methodology consisted of synthesizing several similar preparations and then the comparison of their physiological effectiveness by a pharmacist. One of the first research areas was formed by the salicylic acid derivatives. He described the problems he encountered with his colleague and professor, Dreser, who had been appointed on identical rank. Therefore each depended on the other for fruitful collaboration. He further revealed what had been happening during the period of more than a year in which nothing was heard about acetylsalicylic acid. Clinical research was being performed before Dreser started his pharmacological study, using a network in which Dr Goldmann, Bayer's representative in Berlin, clinically working physicians and Carl Duisberg played an important role. Finally, he explained why Bayer brought this new medicine in tablet form onto the market so quickly.

Many of the details he gave fit more plausibly in the history of Aspirin's origins, as can be seen from the documents in Bayer's archives, than the information published by Bayer suggests. Eichengrün was the boss and defined the research strategy (as indicated in his correspondence with Duisberg). They worked together, in a small place, on the same issue, and used Eichengrün's system of synthesizing several similar preparations (as the lab notebooks show). Animosity between Eichengrün and Dreser was very probable, as Wimmer indicates.<sup>34</sup> He gives an explanation for the fact that clinical research took place before Dreser put his pharmacological experiences on paper and also provides evidence of Dreser using that clinical research in his publications (such as, for example, his pharmacological brochure). Finally he emphasizes the fact that Aspirin was from the start the first remedy sold in tablet form, as is also clear from the accounts of the Pharmaceutical Division meetings.

Unfortunately, Eichengrün's publications on Aspirin for the Deutsche Pharmazeutische Gesellschaft cannot be traced, although a trawl through the 'Berichte' of the Deutsche Pharmazeutische Gesellschaft can be of help in throwing more light on this matter.<sup>35</sup>

Even after Eichengrün's publications the Aspirin question was unresolved. When he died around 1950, articles appeared in the *Pharmazeutische Zeitung*, the clinical magazine *Collier* and the *Chemiker-Zeitung*, in which he was named as the tragic inventor of Aspirin.<sup>36</sup> Later, in 1983, *Die Medizinische Welt* maintained that Arthur Eichengrün was

<sup>31</sup> This lecture was later published: A Eichengrün, '25 Jahre Arzneimittelsynthese', *Zeitschrift für angewandte Chemie*, 24 January 1913, 7: 49–54.

<sup>32</sup> Bayer-Archiv. 27/2.1 Personalakte, Arthur Eichengrün, 'Aspirin' pp. 1-8.

<sup>33</sup> A Eichengrün, '50 Jahre Aspirin', *Pharmazie*, 1949, 4: 582–4.

<sup>34</sup> Wimmer, op. cit., note 16 above, p. 126.

<sup>35</sup> Gunter Drum, *Geschichte der Deutschen Pharmazeutischen Gesellschaft (1890–1986)*, Stuttgart, Deutscher Apotheker Verlag, 1990. On p. 396 Drum mentions that Eichengrün often attended the meetings and joined in the discussions.

## *One Hundred Years of Aspirin*

the actual discoverer of Aspirin. H D Collier also mentions Eichengrün's involvement in the invention of Aspirin.<sup>37</sup> Müller-Jahncke and Friedrich draw attention to Eichengrün's participation in the invention of the drug with their reference to his 1949 article.<sup>38</sup> Jan R McTavish, however, in two excellent articles concerning Aspirin, says nothing of Eichengrün's involvement in the development of the drug.<sup>39</sup>

### **Conclusion**

In this "historical note" the truth in relation to the invention of Aspirin is not given. The objective is only to show that Eichengrün's statement is plausible and merits further examination. Compared with Eichengrün's claim, the story of Bayer, strongly based on the two "heroes" Hoffmann and Dreser, is less credible. Not only is this story not always sustained by the material available in Bayer's archives, it is also not in accordance with Bayer's research-structure, in which communication and supervision played important roles. One-man actions do not fit in with Bayer's structure, where collaboration was of the utmost importance. Eichengrün's version, on the other hand, is based on collaboration within the laboratory and with other persons in and outside the factory.

<sup>36</sup> Bayer-Archiv. A Wiegler, Betr. Erfindung Aspirin, Leverkusen-Bayerwerk 25.8.1959, pp. 6–7.

<sup>37</sup> H O J Collier, 'The story of aspirin', in M J Parnham and J Bruinvels (eds), *Haemodynamics, hormones and inflammation: discoveries in pharmacology*, vol. 2, Amsterdam, Elsevier, 1984, pp. 555–93.

<sup>38</sup> Müller-Jahncke and Friedrich, op. cit., note 1 above, p. 144.

<sup>39</sup> Jan R McTavish, 'Aspirin in Germany: the pharmaceutical industry and the pharmaceutical profession', *Pharm. Hist.*, 1987, **29**: 103–15, and *idem*, 'What's in a name? Aspirin and the American Medical Association', *Bull. Hist. Med.*, 1987, **61**: 343–66.