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The discovery of heroin

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Sept 19, 1998, marks the centenary of the introduction into medicine of heroin by Farbenfabriken vorm. Friedrich Bayer & Co. Understandably, the 623-page history of this renowned German pharmaceutical company makes no mention of what has become the most notorious drug of our time.[1] Yet, heroin was developed by the same research team who introduced aspirin. These researchers were convinced that heroin would make a valuable contribution to medicine as a cough suppressant to assist breathing in patients with severe lung disease. This conviction is reflected in the origin of the drug's name—the German term *heros* refers to an ancient Greek hero who is honoured as a demigod on account of his deeds.[2] The full details of how heroin was developed have never been revealed, but it is possible to speculate about what took place by discussing other developments that occurred around the same time.

Heroin was not an original discovery by the Bayer team. When London-born Augustus Matthiessen, who had studied with Bunsen at Heidelberg, was appointed as lecturer in chemistry at St Mary's Hospital Medical School in London, in 1862, his research focused on the opium alkaloids. Later, he was joined by Charles Alder Wright in a collaboration that led to the discovery of the emetic apomorphine after morphine was heated with hydrochloric acid in a sealed tube.[3] After Matthiessen's death, Wright synthesised several morphine esters in 1874, including acetylcodeine, acetylmorphine, and diacetylmorphine.[4] Tests of the hydrochlorides of these new esters in a dog and a rabbit by the London physician F M Pierce[5,6] were inconclusive, since no direct comparison with morphine was made.

At the Materia Medica Department of the University of Edinburgh during the late 1880s, chemist David Dott and physician Ralph Stockman extended the pioneering studies begun in their department nearly 20 years earlier by Crum Brown and Fraser's research on the biological effects of altering the chemical structures of plant alkaloids.[7] Dott and Stockman investigated diacetylmorphine in frogs and rabbits in 1888,[8] and found it had a much more intense action than morphine. 2 years later, they reported to the British Medical Association[9] that diacetylmorphine was not only more effective than morphine in depressing the spinal cord and respiratory centre in frogs and rabbits, it also had a weaker narcotic action. High doses of diacetylmorphine were also more likely than morphine to induce convulsions. The prime concern of their report, however, was the effect of chemical structure on pharmacological activity, and they did not seem to be interested in any therapeutic potential of the new compound.

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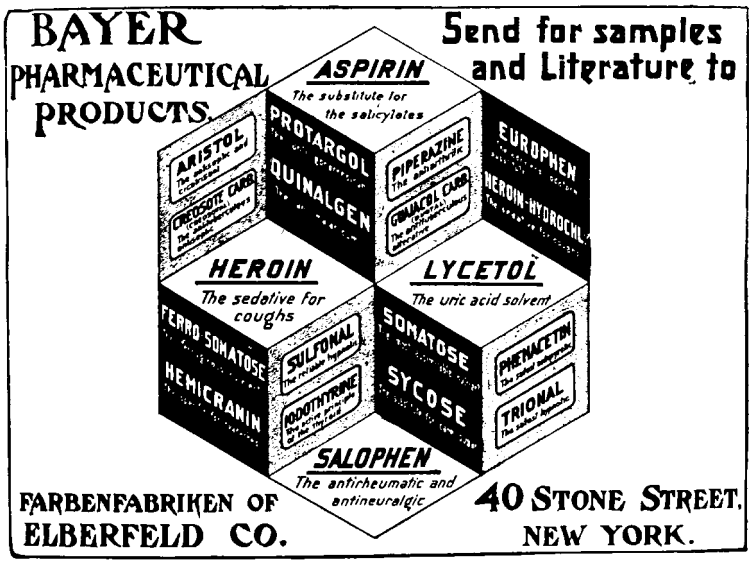
It was not until 1898 that further reference was made to the pharmacological activity of diacetylmorphine. Joseph von Mering,[10] a physician who was to become famous for his discovery of the hypnotic barbiturates,[11] included the drug among 18 morphine derivatives that he tested for the alkaloid manufacturer E Merck of Darmstadt who had used a method devised by Hesse[12] to synthesise the drug. von Mering corroborated the findings of Stockman and Dott and confirmed the same pharmacological effects in dogs. He went on, however, to report that his many clinical observations showed that diacetylmorphine was weaker than morphine in its ability to suppress coughing and was far less effective as an analgesic. During the previous summer, von Mering had tested diacetylmorphine without success in patients with advanced pulmonary tuberculosis. He also suggested that diacetylmorphine hydrochloride was unsuitable for use in the clinic because of its chemical instability and insufficient solubility in water to allow formulation as a subcutaneous injection. von Mering was clearly mistaken about the question of solubility, since 1 g diacetylmorphine hydrochloride dissolves in 1·6 mL water. The issue of chemical instability could have been dealt with by dissolving the contents of a sealed container in water immediately before use.



AKG, London

Bayer advertisement for heroin, 1900

von Mering did not reject all the compounds he received from Merck. He was particularly impressed with ethylmorphine, a compound synthesised by Grimaux in 1881,[13] which he found to be efficacious in the alleviation of coughs, even in patients with pulmonary tuberculosis in whom codeine had proven ineffective. In January, 1898, Merck marketed ethylmorphine as a cough suppressant, under the proprietary name of dionin. Initial expectations of this drug were high and it was hailed as superior to codeine, though nowadays it is rarely prescribed. Ethylmorphine was the first semi-synthetic morphine

derivative to be introduced into the clinic and must have influenced the subsequent decision of F Bayer & Co to introduce heroin for similar clinical purposes.

The pharmaceutical science department of Bayer had successfully marketed the antidiarrhoeal preparation tannigen in 1894. This drug was a semi-synthetic tannic-acid derivative in which two of its phenolic hydoxyl groups had been acetylated. Bayer claimed that the acetylation had removed the irritancy caused by the astringent action of tannic acid on the linings of the mouth and stomach. When exposed to the mild alkalinity of the small intestine, tannigen was hydrolysed, allowing the released tannic acid to exert its astringent action in situ. By 1907, the drug had received the approved name of acetannin and appeared in pharmacopoeias throughout the world; tannigen ceased to be popular only when the use of tannins to control diarrheoa went out of fashion during the 1950s.

Shortly before marketing tannigen, Bayer introduced salophen, a salicylic-acid derivative in which the carboxylic acid group had been masked by esterification with paracetamol in an attempt to reduce the irritant action on the stomach lining.[14] Salophen remained in use as an antipyretic, antirheumatic analgesic until the 1960s, but it never rivalled aspirin in popularity. When Arthur Eichengrün was appointed as Bayer's head of the pharmaceutical science laboratory at Elberfield, in 1895, he continued the salicylate study by masking the phenolic hydroxyl group in salicylic acid rather than its carboxylic-acid function.[15] Eichengrün's work was in line with the earlier approach used in the case of tannigen. To achieve this objective, the phenolic hydroxyl group in salicylic acid had to be reacted with an alkyl or acyl group. Among the compounds then prepared by Eichengrün's assistant, Felix Hoffmann, was acetylsalicylic acid, later marketed as aspirin.[16]

Hoffmann recorded in his laboratory notebook that he synthesised diacetylmorphine on Aug 21, 1897,[17] 2 weeks after he had synthesised acetylsalicylic acid.[15] A reasonable assumption is that Eichengrün had decided that morphine should be acetylated for much the same reason as tannic and salicylic acids, namely to avoid the common side-effects of nausea and vomiting. He certainly was not influenced by the introduction of dionin, since it did not take place until 4 months later. von Mering's paper on morphine derivatives had not yet been published so Eichengrün would not have known that diacetylmorphine had been rejected. de Ridder[17] and Schadewald[18] postulated that the instigator of the synthesis of diacetylmorphine was Heinrich Dreser, who was appointed head of the Bayer pharmacology laboratory in 1897. This suggestion is unlikely since only 2 weeks elapsed between the syntheses of acetylsalicylic acid and diacetylmorpine by Hoffmann. Furthermore, at that time Dreser was not convinced of the value of acetylsalicylic acid.[15]

Dreser began his research on diacetylmorphine in rabbits, but soon moved on to human beings; his main concern was to assess its value as a substitute for codeine in severe coughing. Dreser reported his findings to the Congress of German Natural Scientists and Physicians in Düsseldorf on Sept 19, 1898.[19] That same month, a communication from Dreser and the Bayer company physician, Theobald Floret, appeared in *Therapeutische Monatschefte*.[20] A more detailed account was subsequently published,[21] which was the most extensive scientific paper yet to have emerged from any industrial pharmacology laboratory. In none of these papers, however, did Dreser refer to the previous publications of Wright and Pierce or Dott and Stockmann, nor did he acknowledge the key contribution of Eichengrün and Hoffmann.

The papers by Dreser reveal that studies in rabbits had convinced him that diacetylmorphine, in addition to relieving cough, was uniquely able to both slow and deepen respiration. Investigations on volunteers and patients seemed to confirm this finding and led Dreser to conclude that the new drug would be of immense value in severe respiratory disease since it is not only suppressed cough but could even assist in clearing the lungs of excess phlegm and other matter. Convinced that the value of the new drug lay in its combination of cough-suppressant activity with a stimulant action on the respiratory system, Bayer registered the name heroin in June, 1898. Higby[22] described how the company's belief that it had a highly specific stimulant action on the lung was enthusiastically confirmed by many physicians. A parallel was even drawn between the action of digitalis on the heart and heroin on the lung, both being judged to be drugs with a highly specific action of slowing the activity of their target organ while increasing its strength.[23]

When heroin was launched in September, 1898, Farbenfabriken vorm. Friedrich Bayer & Co made no attempt to suggest that it had any clinical role other than to afford relief in respiratory disease. An early clinical survey in the USA concluded that heroin was inferior to morphine as an analgesic,[24] a view reflected in the monograph on acetomorphine (the original approved name for heroin) in the *British Pharmaceutical Codex* of 1907:

> "Acetomorphine resembles morphine in its action in allaying peripheral irritation and relieving pain. The introduction of acid (or alkyl) groups into the morphine molecule, however, weakens, though it does not remove, its depressing action on the respiratory centre, and lessens its narcotic effect. Acetomorphine thus resembles codeine, and is much employed to relieve irritable cough, especially in phthisis, asthma and bronchitis with dyspnoea. Its use is not followed by headache, and it does not usually constipate. Glycerinum Acetomorphinae and Elixir Acetomorphinae Compositum are valuable preparations to allay cough, the latter combining with acetomorphine the expectorant properties of terpin hydrate."[25]

This extract shows that the claim of a stimulant action on the respiratory centre had by then been dismissed, but it was not until 1911 that von Issekutz[26] published evidence to show that Dreser had been mistaken. Heroin actually had depressive effects on the respiratory system and so its action was qualitatively similar to that of morphine, codeine, and ethylmorphine. The monograph in the *British Pharmaceutical Codex* which appeared that same year added a cautionary phrase before its reference to the treatment of irritable cough:

> "acetomorphine resembles codeine, *over which it is very doubtful if it possesses any advantage:* it is much employed to relieve irritable cough especially in phthisis, asthma and bronchitis, with dyspnoea".

After nearly 12 years of use, the clinical rationale for the introduction of heroin was being challenged.

Since heroin is about twice as potent a cough suppressant as morphine, the small oral doses required for cough suppression would probably have produced habituation in only a few patients when it was first introduced.[28] Higby[22] argued that since heroin was mainly administered in cases of chronic lung disease, medication would have been continued, thereby hiding withdrawal symptoms.[22] Thus, for a time heroin acquired the reputation of being no more addictive than codeine.

However, the 1911 edition of the *British Pharmaceutical Codex* observed that it was nearly as easy to become addicted to the habit of taking acetomorphine as morphine.

The question of addiction became a matter of widespread public concern in the USA after the publication, in 1912, of a report by Phillips,[29] a physician who cited cases of heroin addiction among people who sniffed the drug in a similar manner to that of cocaine. Addicts had exploited the absence of any legislation to restrict the sale of the supposedly non-addictive heroin.[29] The drug was more readily available over the counter than codeine, was more potent than morphine, and so allowed small quantities to be hidden by addicts, which could be sniffed, smoked, swallowed, or injected.[22] In the latter case, the higher water solubility of heroin compared with that of morphine salts facilitated street use of the drug. These factors, coupled with antiGerman sentiment during the years leading to the entry of the USA in World War 1, roused professional and public resentment at the free availability of heroin. In December, 1914, Congress passed the Harrison Act that introduced federal narcotic controls and limited the maximum amount of heroin in proprietary preparations to less than 10 mg per g of product. Although a few physicians campaigned to retain their right to administer heroin to addicts and others,[30] most no longer prescribed the drug after 1915, although an outright ban was not introduced until 1924.[22] Many other countries also decided to ban the medical use of heroin, but not the UK.

The epidemic of heroin abuse recorded in the USA during the early years of this century did not occur in the UK. In 1926, a Ministry of Health report on morphine and heroin addiction[31] noted that the incidence of opiate dependence in the UK was low, and in only the rarest of cases was heroin involved. The 1934 edition of the *British Pharmaceutical Codex*,[32] which referred to heroin by its revised approved name of diamorphine, certainly acknowledged the American experience by warning that the effects of addiction were worse than those of morphine and could lead to "greater mental and moral degradation occurring". While firm legislative action in the UK was taken to control the use of diamorphine, there was no public outcry as in the USA, and so no outright ban was introduced. The need for caution was certainly recognised, the 1954 edition of the *British Pharmaceutical Codex* gave a strongly worded warning: "It should be used with great caution and only when less dangerous analgesics and cough suppressants have proved inadequate or unsuitable".[33]

That Bayer would have marketed diacetylmorphine in 1898 had Dreser not been mistaken about its effects on respiration is unlikely. At that time, there was no evidence to suggest it had any other advantage over morphine. However, the 1963 edition of the *British Pharmaceutical Codex* included an analgesic formulation, namely injection of diamorphine "for subcutaneous injection in a dose of 5 to 10 milligrams for the relief of pain and restlessness in the terminal stages of carcinoma and other fatal illnesses".[34] 10 years later, the *British Pharmaceutical Codex* added the comment that, in such situations diamorphine could also be given by mouth in conjunction with cocaine.[35]

Clinical acceptance of diamorphine now exists, but tragically this drug that can bring relief to tortured bodies has itself tortured the bodies of many who have chosen to misuse it. Blame should not be laid at the door of those who initiated the development of the drug. Although Bayer unquestionably intended to make a profit from its research, the Bayer Company introduced heroin because it believed the drug would be of benefit to the sick. The pharmacology of heroin may have been suspect, not its intended role.

References

1 Verg E. Milestones. Leverkusen: Bayer AG, 1988.
2 Das Fremdwörterbuch. Der Brosse Duden in 10 Bänden, vol 5. Mannheim: Bibliographisches Institut AG, 1966: 271.
3 Matthiessen A, Wright CRA. On the action of hydrochloric acid on morphine. *Proc R Soc Lond* 1869; **17:** 455–60.
4 Wright CRA. On the action of organic acids and their anhydrides on the natural alkaloids: part I. *J Chem Soc* 1874; **27:** 1031–42.
5 Pierce FM. On the physiological action of the above morephine and codeine derivatives. *J Chem Soc* 1874; **27:** 1043–44.
6 Pierce FM. On the physiological action of some new morphine and codeine derivatives. *Practitioner* 1975; **14:** 437–42.
7 Crum Brown A, Fraser TR. On the physiological action of the salts of the ammonium bases derived from strichnia, brucia, thebeia, codeia, morphia, and nicotia. *Trans R Soc Edin* 1868; **25:** 151–204.
8 Dott DB, Stockman R. The chemitry and pharmacology of some of the morphine derivatives. Year book of pharmacy. London: Churchill, 1888: 349–55.
9 Stockman R, Dott DB. Report on the pharmacology of morphine and its derivatives. *BMJ* 1890; ii: 189–92.
10 von Mering J. Physiological and therapeutic investigations on the action of some morphia derivatives. *The Merck Report* 1898; **7:** 5–13.
11 Sneader W. Drug prototypes and their exploitation. Chichester: Wiley, 1996: 185–87.
12 Hesse O. Studien über morphia. *Annalen* 1884; **222:** 206.
13 Girmaux E. Sur la transformation de la morphine en codéine et en bases homologues. *Compt Rend Acad Sci Paris* 1881; **92:** 1140–43.
14 Siebel W. Pharmakologische untersuchungen über salophen, ein seues salicylsaürederivat *Therap Monatsh* 1892; **6:** 31–35.
15 Eichengrün A. 50 Jahre Aspirin. *Pharmazie* 1949; **4:** 582–84.
16 Sneader W. The discovery of aspirin. *Pharm J* 1997; **259:** 614–17.
17 de Ridder M. Heroin: new facts about an old myth. *J Psychoactive Drugs* 1994; **26:** 65–68.
18 Schadewaldt H. Historical aspects of pharmacologic research at Bayer 1890–1990. *Stroke* 1990; **21** (suppl IV): 15–18.
19 Dreser H. Pharmakologisches über einige Morphinderivat. *Deut Med Wochenschr* 1898; **24:** 185.
20 Dreser H, Floret T. Pharmakologisches ueber einige morphinderivate. *Therap Monatsch* 1898; **12:** 509–12.
21 Dreser H. Ueber die wirkung einiger derivative des morphines auf die athmung. *Arch Ges Physiol* 1898; **72:** 485–521.
22 Higby GJ. Heroin and medical reasoning: the power of analogy. *NY State J Med* 1986; **86:** 137–42.
23 Leo H. Ueber den therapeutischen Werth des Heroins. *Deut Med Wochenschr* 1899; **25:** 186.
24 Manges M. A second report on the therapeutics of heroin. *NY Med J* 1900; **71:** 51–54, 79–83.
25 British Pharmaceutical Codex. London: Pharmaceutical Society; 1907: 8.
26 von Issekutz B. Über die wirkung des codeins, dionins und heroins auf die atmung. *Arch Ges Physiol* 1911; **142:** 255–67.
27 British Pharmaceutical Codex. London: Pharmaceutical Press, 1911: 8–9.
28 Eddy NB. Heroin laboratory and clinical evaluation. *Bull Nac* 1953; **5:** 43.
29 Phillips J. Prevalence of the heroin habit. *J Am Med Assoc* 1912; **59:** 2146–47.
30 Musto DF. The American dream. London: Yale University Press, 1973: 91–120.
31 Ministry of Health. Departmental Committee on Morphine and Heroin Addiction. Report (The Rolleston Report). London: HM Stationery Office, 1926.
32 British Pharmaceutical Codex. London: Pharmaceutical Press, 1934: 390–91.
33 British Pharmaceutical Codex. London: Pharmaceutical Press, 1954: 236–37.
34 British Pharmaceutical Codex. London: Pharmaceutical Press, 1963: 243–44.
35 British Pharmaceutical Codex. London: Pharmaceutical Press, 1973: 153.