

because it was operative; the physician-accoucheurs claimed that obstetrics and gynaecology belonged together. As we know, the surgeons won the argument. By the 20th century the obstetrician-gynaecologist (who often, but not necessarily, possessed the FRCS) became another kind of doctor who was always addressed as Mr. And this is more or less the position today; but is the persistence of this tradition sensible?

Fifty years ago it was relatively simple. Physicians treated medical diseases and surgeons operated. Today, the treatment of surgical disorders is often undertaken by teams of doctors any of whom may “intervene” in a technical or surgical manner (the interventional radiologists are an example), whether they are titled Dr or Mr, Miss, Mrs, or Ms. Thus patients with cancer who happen to be sticklers for addressing people correctly may well be puzzled when they are referred by Dr A, their general practitioner, to Dr B, an oncologist, and Dr C, a radiologist, before seeing Mr or Ms D, a surgeon. An operation is performed under an anaesthetic administered by Dr E after which the patient is referred to Dr F for radiotherapy and back to Dr B for chemotherapy depending, perhaps, on the findings of a pathologist, Dr G. Further, the patient may enter a controlled trial run by a medical statistician, Dr H, who is not medically qualified but has a PhD.

That is eight “Drs” to one “Mr (or Miss or Mrs or Ms).” Note that any of these doctors, including Mr B, might possess an MD or a DM, which often puzzles American doctors who are not always aware that in the United Kingdom these are postgraduate degrees. But whether or not they have been awarded a university doctorate (an MD, DM, DPhil, or PhD) is irrelevant to how they are addressed. Only the surgeon is addressed as Mr (or Miss or Mrs or Ms), together with his or her

registrar; but the house surgeon is not, for it is (or used to be) considered bad form if Dr John Jones who was a house physician yesterday insists on being called Mr Jones when taking up the house surgeon post tomorrow.

Medical qualifications in the United Kingdom have been in an unholy muddle ever since the Medical Act of 1858 when no less than 18 independent medical institutions offered a range of bachelorships, licences, diplomas, memberships, fellowships, and doctorates all officially recognised by the General Medical Council. This cannot be altered. Now, however, so much of surgery is teamwork that it seems to me that the original and rather trivial reasons for “mistering” surgeons have disappeared. Would surgeons be willing to abandon this pretentious anachronism so that all who possess a medical qualification that is recognised by the General Medical Council, regardless of the specialty and the letters after their name, are simply addressed as Dr? It is at least worth considering.

Competing interests: None declared.

- 1 Aronson J. Modern English abuse. *BMJ* 2000;320:357.
- 2 Cope Z. *The Royal College of Surgeons of England: a history*. London: Anthony Blond, 1959.
- 3 Royal Society of Medicine London. *The notebooks of John Greene Crosse of Norwich*. MS 1812;285:g.11. (Manuscript collection.)
- 4 Report of the Select Committee on Medical Education. Evidence of G J Guthrie, PRCS. *Parliamentary Papers* 1834;XIII (part 2):Q4842.
- 5 Loudon I. *Medical care and the general practitioner, 1750-1850*. Oxford: Clarendon Press, 1986:152-70.
- 6 Loudon I. Medical education and medical reform. In: Nutton V, Porter R, eds. *The history of medical education in Britain*. Amsterdam: Rodopi, 1995:229-49.
- 7 Cooke AM. *A History of the Royal College of Physicians*. Vol 3. Oxford: Clarendon Press, 1972:844-60.
- 8 Report of the Select Committee on Medical Education. Evidence of G J Guthrie, PRCS. *Parliamentary Papers* 1834;XIII (part 2):Q4731.
- 9 Loudon I. *Death in childbirth: an international study of maternal care and maternal mortality, 1750-1850*. Oxford: Clarendon Press, 1992:183.

The discovery of aspirin: a reappraisal

Walter Sneider

The discovery of aspirin is customarily said to have resulted from Felix Hoffmann's rheumatic father encouraging his son to produce a medicine devoid of the unpleasant effects of sodium salicylate. Hoffmann, a chemist in the pharmaceutical laboratory of the German dye manufacturer Friedrich Bayer & Co in Elberfeld, consulted the chemical literature and came across the synthesis of acetylsalicylic acid and then prepared the first sample of pure acetylsalicylic acid on 10 August 1897. This was marketed in 1899 under the registered trademark of Aspirin. This account of the discovery first appeared in 1934 as a footnote in a history of chemical engineering written by Albrecht Schmidt, a chemist who had recently retired from IG Farbenindustrie—the organisation into which F Bayer & Co had been incorporated in 1925.¹

Challenge to the accepted account

The footnote also stated that Hoffmann had arranged for several chemical derivatives of salicylic acid to be

Summary points

Until now, it has been generally accepted that Felix Hoffmann developed aspirin to help his rheumatic father

In 1949 Hoffman's former colleague Arthur Eichengrün claimed that the work had been done under his direction

Analysis of relevant archival and published material now supports Eichengrün's claim and throws doubt on the reliability of the source crediting Hoffmann

It is likely that acetylsalicylic acid was synthesised under Eichengrün's direction and that it would not have been introduced in 1899 without his intervention

Department of
Pharmaceutical
Sciences, University
of Strathclyde,
Glasgow G4 0NR
Walter Sneider
deputy head
w.sneider@strath.
ac.uk

BMJ 2000;321:1591-4



BAYER AG

examined, not just its acetyl ester. No indication was given of what the others were, but in 1899 Heinrich Dreser, head of the experimental pharmacology laboratory at Elberfeld, named them in a paper as propionyl, butyryl, valeryl, and benzoyl salicylic acids.² He further alluded to them in 1907,³ and again in 1918.⁴ No earlier reports of the preparation of any of these are to be found, but three of them appear in a British patent awarded on 3 March 1900 to Hoffmann's colleague Otto Bonhoeffer,⁵ and there is also a United States patent for propionylsalicylic acid, again in the name of Bonhoeffer.⁶ The award of these patents is indicative of the absence of any prior mention of these compounds in the literature. It must therefore be concluded that the 1934 footnote is unreliable since it clearly stated that Hoffmann had examined "preparations of salicylic acid derivatives which remained unnoticed amongst several prepared a long time before for other purposes." The patents show that the derivatives were newly prepared for the specific purpose of finding a salicylic acid derivative that would be of therapeutic value. Is then the remainder of the footnote to be believed?

Laboratory reports of Hoffmann and Dreser

The page on which Hoffmann reported his synthesis of pure acetylsalicylic acid in 1897 is retained in the archives of Bayer AG in Leverkusen. The significance of the final sentence on it—"Durch ihre physikalischen Eigenschaften wie eine sauren Geschmack ohne jede Ätzwirkung unterscheidet sich die Acetylsalicylsäure

vorteilhaft von der Salicylsäure und wird dieselbe in diesem Sinne auf ihre Verwendbarkeit geprüft"—has been overlooked.

The correct translation is: "Due to its physical properties, such as an acid taste without any corrosive action, acetylsalicylic acid differs advantageously from salicylic acid and is being examined for its usefulness with just this in mind." The German is, however, grammatically awkward and the sentence is capable of being misread to mean that the compound was about to be tested rather than that it was being tested. The most likely interpretation, however, is that testing of acetylsalicylic acid was already taking place at the time Hoffmann wrote.

In a commemorative volume marking Bayer's 50th anniversary Arthur Eichengrün, a colleague of Hoffmann, pointed out that after examining acetylsalicylic acid Dreser had set it aside for nearly 18 months until he once again became involved with it in 1898.⁷ This statement was never disputed by Dreser, who contributed the next article in the same publication.⁴ A recent Bayer publication notes, too, that Hoffmann had repeatedly told his colleagues that Dreser had set acetylsalicylic acid aside.⁸ Because Dreser did not begin to write laboratory reports until 16 May 1898 there is no record of his testing salicylic acid derivatives in 1897. However, his laboratory notebook shows that on 27 September 1898, and three more times that year, he investigated acetylsalicylic acid on its own. If there was an interval of nearly 18 months between Dreser's first and later experimenting with acetylsalicylic acid, this interval obviously could not have ended much before 27 September 1898, since he took up his appointment at Elberfeld on 1 April 1897. His initial work testing salicylic acid derivatives must have been soon after his arrival there.

His laboratory reports from 27 September 1898 onward do not reveal why Dreser was then testing acetylsalicylic acid on its own rather than with the other four derivatives named in his 1899 paper. Something must have induced him to single out acetylsalicylic acid, and the explanation can be found in a paper written by Eichengrün.

The claims of Arthur Eichengrün

In a paper published in *Pharmazie* in 1949, Eichengrün claimed that he had instructed Hoffmann to synthesise acetylsalicylic acid and that the latter had done so without knowing the purpose of the work.⁹ Five years earlier, while in Theresienstadt concentration camp, he had typed a letter (now in the Bayer archives) with wording similar to his 1949 paper.¹⁰ Eichengrün wrote that his objective had been to obtain a salicylate that would not give rise to the adverse effects (gastric irritation, nausea, or tinnitus) frequently associated with sodium salicylate. He was present when the derivatives of salicylic acid were tested by Dreser and came to the conclusion that acetylsalicylic acid was superior to all the other compounds. At a management meeting, Eichengrün called for clinical studies to be initiated, but Dreser used his right of veto as head of the pharmacology division. He believed, mistakenly, that the drug was harmful to the heart.

Convinced of the potential of acetylsalicylic acid, Eichengrün tested it on himself, experiencing no ill

effects. He stated that he then surreptitiously gave a supply of it to his colleague Dr Felix Goldmann, who then recruited physicians to evaluate the drug in strict secrecy. Their reports were most encouraging. Tinnitus was rare, while the antirheumatic effects were unmistakable. But there was more—a dentist had given the drug to a patient with a raised temperature as well as toothache. Hardly was he out of the chair before he exclaimed, “My toothache’s gone!” Such a rapid onset of analgesia was unique. After a similar response was confirmed in other patients, Goldmann sent a report to the Bayer management. According to Eichengrün, when Dreser was asked to comment, he scribbled on it, “This is the usual loud-mouthing of Berlin—the product has no value.”

Eichengrün goes on to tell us that Carl Duisberg, the renowned head of research for Bayer, had ordered Dreser’s results to be checked by an independent pharmacologist. This intervention might explain why Hoffmann synthesised stable, pure acetylsalicylic acid on 10 August 1897. If the meaning of the last sentence in Hoffmann’s report is that acetylsalicylic acid was already under test at that time, it would be consistent with all that Eichengrün has written. Had acetylsalicylic acid been tested along with the other salicylic acid derivatives in April 1897, there would have been no written record of its original synthesis, since Hoffmann did not write any reports between 13 March 1896 and 5 May 1897. Significantly, in none of his laboratory reports did he mention the synthesis of any of the other salicylates known to have been tested by Dreser. Presumably they were prepared for evaluation in April 1897.

In his 1949 paper Eichengrün went on to claim that acetylsalicylic acid was sent to several leading clinics for expert assessment. Confirmation of this claim is found in the first published clinical report on aspirin by Kurt Witthauer of the Deaconess Hospital in Halle, which appeared in the April 1899 issue of *Die Heilkunde*.¹¹ Revealingly, Witthauer remarked, “After long hesitation, the factory was able to be convinced by my favourable experiences to bring aspirin on to the market.” Further light is thrown on this statement by Friedrich Fischer, the head of the Elberfeld pharmaceutical laboratory in 1897, when he wrote that Witthauer had energetically pushed for the introduction of the drug owing to its excellent success in the clinic.¹² It should be noted that Witthauer stated that he had received the new salicylate compound nearly one year earlier—that is, around April 1898.

Eichengrün claimed that Dreser was then instructed to write a report that would give scientific credibility to the new drug. This explains why Dreser reinvestigated acetylsalicylic acid on its own in September 1898.

The credibility of the claims by Eichengrün

Why did Eichengrün wait 15 years before refuting what had been written in 1934 about the role of Hoffmann? The answer may be found by considering Eichengrün’s situation at that time. After the introduction of aspirin, he had developed not only several more drugs but also cellulose acetate, acetate silk, and acetate safety film before leaving Bayer in 1908 to establish his own factory in Berlin. There, he produced flame resistant materials based on acetyl cellulose and also pioneered

the process of injection moulding of plastics. Consequently, he enjoyed the affluent life style of a successful industrialist, yet because he was a Jew all this was put at risk after the Nazi party gained power.

By the time the claim that Hoffmann had initiated the development of aspirin was published, the Nazis had banned Jews from the civil service and from independent positions in the professions and in economic life. Even as a prominent industrialist, Eichengrün was not exempt from their attentions. He was forced to take an associate into his company to avoid loss of contracts from state enterprises. A low profile was the order of the day, but that was not enough to prevent his company being forcibly transferred to another owner in 1938. His marriage to an “Aryan” wife enabled him to retain his freedom until 1944, when at the age of 76 he was interned for 14 months in Theresienstadt, languishing there until its liberation by the Soviet Army.

During the Nazi era, Eichengrün was in no position to issue a public rebuttal of what had been published about Hoffmann. Some insight into his feelings at that time is given by a paragraph in his 1949 paper: “In 1941, there stood in the Hall of Honour of the chemical section of the German Museum in Munich a showcase filled with white crystals, with the inscription, ‘Aspirin: inventors Dreser and Hoffmann’. Dreser had nothing whatsoever to do with the discovery, and Hoffmann carried out my chemical instructions in the first place without knowing the aim of the work. Next to the showcase was a similar one filled with acetylcellulose, today also a product of worldwide importance, whose discovery by me it is impossible to doubt since it was established in a series of German patents from 1901 to 1920. It was simply described by the expression ‘Acetylcellulose—Cellit’; they had refrained from naming the inventor. But, at the main entrance to the museum there hung a large sign which forbade non-Aryans from entering this institute! Those who understand will read between the lines.”

In his letter from Theresienstadt, Eichengrün concluded a similar paragraph with a different sentence: “To what influences this omission is to be attributed, can be only assumed.” There can be little doubt that he felt that he had been written out of history because he was a Jew. Such historical revisionism was not unknown in the Nazi era.

Two years after the war ended, Eichengrün celebrated his 80th birthday amid glowing tributes in German scientific journals.^{13–15} He died in Berlin on 23 December 1949, in the same month that his account of the discovery of aspirin was published. He was spared from knowing that it would remain largely ignored for another half century.

Conclusion

Everything that Eichengrün claimed in 1949 about the discovery of aspirin is compatible with the chronology of events presented here, which in turn depends to a great extent upon the reliability of the statement by Eichengrün that Dreser set acetylsalicylic acid aside for 18 months. This statement, however, has never been challenged. As Eichengrün did not refer to his own role in the discovery of aspirin in the chapter in which the statement appeared in 1918, it would be unreasonable

to argue that the source is tainted. Also, Hoffmann—who lived until 1946 without ever publishing his own account of the discovery of aspirin—repeatedly spoke of Dreser setting the drug aside, albeit without indicating for how long. But had it only been for a short period, he would not have mentioned it.

In deciding whether it is Hoffmann or Eichengrün who initiated the events leading to the introduction of aspirin, the unreliability of the 1934 footnote about Hoffmann must be balanced against the plausibility of the 1949 paper by Eichengrün. The most reasonable conclusion is that Arthur Eichengrün was telling the truth when he wrote that acetylsalicylic acid was synthesised under his direction and that the drug would not have been introduced in 1899 without his intervention.

F Bayer & Co was truly fortunate in having Eichengrün as an employee, yet it is unlikely that he would have discovered aspirin had he not been working for the company. Its successor, Bayer AG, had every reason last year to celebrate proudly the centenary of the most widely used drug in history.

I thank M Frings and H-H Pogarell of Bayer-Archiv, Leverkusen, as well as their former colleague Dr M Busch, for valuable assistance throughout the course of my investigations and visits to the archive. I am also indebted to Joan Girling for the translation of the paper in *Pharmazi*.

Funding: None.

Competing interests: None declared.

- Schmidt A. *Die industrielle Chemie in ihrer Bedeutung im Weltbild und Erinnerungen an ihren Aufbau*. Berlin: De Greuter, 1934:775.
- Dreser H. Pharmakologisches über aspirin (Acetylsalicylsäure). *Pflügers Arch* 1899;76:306-18.
- Bayer-Archiv. Pharmakologisches Labor Elberfeld. 103/12.1. Prof Dreser, 27.07.1907. Die pharmakologische Laboratorium der Farbenfabriken, pp 6-7.
- Dreser H. Das pharmakologische Laboratorium der Farbenfabriken. In: *Geschichte und Entwicklung der Farbenfabriken vorm Friedr Bayer & Co, Elberfeld, in den ersten 50 Jahren*. Munich: Meisenbach-Riffraath, 1918:419-24.
- Bonhoeffer O. The manufacture or production of acidyl salicylic acids. British Patent 9123, 3 March 1900.
- Bonhoeffer O. Propionyl-salicylic acid and process of making same. US Patent 656435, 21 August 1900.
- Eichengrün A. Pharmaceutisch-wissenschaftliche Abteilung. In: *Geschichte und Entwicklung der Farbenfabriken vorm Friedr Bayer & Co, Elberfeld, in den ersten 50 Jahren*. Munich: Meisenbach-Riffraath, 1918:409-16.
- Zündorf U. 100 Years of aspirin : the future has just begun. Leverkusen: Bayer, 1997:33.
- Eichengrün A. 50 Jahre Aspirin. *Pharmazie* 1949;4:582-4.
- Bayer-Archiv. 271/2.1 Personal data on Eichengrün. Dr A. Eichengrün, Aspirin, KZ Theresienstadt, 1944:2.
- Witthauer K. Aspirin, eine neues Salicylpräparat. *Die Heilkunde* 1899;3:396.
- Fischer F. Die Pharmazeutischen Betriebe. In: *Geschichte und Entwicklung der Farbenfabriken vorm Friedr Bayer & Co, Elberfeld, in den ersten 50 Jahren*. Munich: Meisenbach-Riffraath, 1918:427-36.
- Stadlinger H. Gedenktage. Dr Ing eh, dr phil Arthur Eichengrün 80 Jahre. *Pharmazie* 1947;2:383-4.
- Escales E. A Eichengrün 80 Jahre. *Kunststoffe* 1947;37:180.
- Bodenbender HG. A Eichengrün zum 80 Geburtstag. *Angewandte Chemie* 1948;60:111-2.

Serial homicide by doctors: Shipman in perspective

Herbert G Kinnell

18 Cross Street,
Reading, Berkshire
RG1 1SN
Herbert G Kinnell
retired consultant
psychiatrist

BMJ 2000;321:1594-7

The previous BMA chairman, among others, is on record as saying that Harold Shipman is unique, yet medicine has arguably thrown up more serial killers than all the other professions put together, with nursing a close second.¹⁻⁴ Dentistry too has had its notorious characters, yet among veterinarians homicide seems to be almost unknown.

“Jack the Ripper,” the perpetrator of five unsolved murders in 1888 in London, is thought to have been a member of the medical profession, although there is no conclusive evidence. Sir William Gull, “physician in ordinary” to Queen Victoria, and Dr Thomas Barnardo were prime suspects, and there were advocates for Montague John Druitt, a barrister (he was from a respected medical family and may have passed himself off as a doctor); a Dr Stanley (he may have been fictitious); the Polish Dr George Chapman (real name Severin Klosowski); and the Russian Dr Alexander Pedachenko.⁵⁻⁷ Nor has conclusive evidence been found for Gaylord Sundheim (a psychotic who had studied medicine) being the “mad butcher” of Cleveland, Ohio, in the 1930s.⁸

The power of life and death

Yet there are enough recorded instances of multiple murders by doctors (real or bogus) to make at least a prima facie case that the profession attracts some

Summary points

Arguably medicine has thrown up more serial killers than all the other professions put together

The medical profession seems to attract some people with a pathological interest in the power of life and death

Doctors have been responsible for killing not only patients and strangers but members of their own family

The political killers par excellence were the Nazi doctors and the Japanese doctors engaged in biological warfare

people with a pathological interest in the power of life and death. Would be doctors with homicidal tendencies include Kenneth Bianchi, one of the serial “Hillside Stranglers” in 1978 (his cousin was the other murderer), who had always wanted to be a psychiatrist and indeed set himself up as a psychological counsellor after assuming a false identity,⁹ and William Henry Theodore Durrant, a San Francisco medical student and Sunday school superintendent who