CROSSROADS: WHERE MEDICINE AND THE HUMANITIES MEET

Physicians, Fads, and Pharmaceuticals: A History of Aspirin

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* To whom correspondence should be addressed: Faculty of Medicine, McGill University, 3655 Drummond St., Montreal, QC, Canada H3G 1Y6"Politics is not out there in society.

Politics is down there in the laboratory."

--Bruno Latour (1).

Aspirin is a product of the late-nineteenth-century laboratory, pharmaceutical industry, and medical community. The prevailing scientific techniques, industrial approaches, and medical beliefs were instrumental in the development, promotion and reception of the drug. As a result, the present account does not extend further back than a few decades prior to the release of aspirin from the laboratories of Farbenfabriken vormals Friedrich Bayer & Co. in 1899. In contrast, much of the current literature on aspirin (2,3,4) attempts to trace the compound back to antiquity through the Ebers papyrus, the Hippocratic writings, and the works of Galen. Such histories tell a simple, linear tale of the numerous "discoveries" proposed to have led to the use of certain salicylate-containing plants, such as willow bark and wintergreen, or salicylate-related compounds, including salicilin and salicylic acid, as cures for a variety of ailments. Indeed, according to Mann and Plummer:

> Both [salicilin and salicylic acid] attacked fever and pain, and their partisans advocated the salicylates' use as antiseptics, mouthwashes, and water preservatives for ocean voyages; one important chemist further suggested (erroneously) that sodium salicylate, a chemical relative, would successfully treat scarlet fever, diphtheria, measles, syphilis, cholera, rabies and anthrax (5).

However, it is difficult to establish what effect, if any, these examples of the "historical" uses of "proto-aspirin" had on the impetus for and modes of developing and using the actual drug called aspirin. As a matter of course, aspirin is usually described as the natural descendant from these salicylate forefathers. However, the history of aspirin is not as straightforward a tale as conventional histories suggest, but rather is a complex narrative of the people and circumstances involved in transforming a simple chemical compound into a popular pharmaceutical product that has remained one of the most widely consumed drugs for almost a century.

Bayer began in 1863 as Friedrich Bayer & Co., a dye-manufacturing plant in Germany. When the dye industry began to wane during the late 1880s, Bayer made the transition into the more active and lucrative

sector of pharmaceuticals by developing, producing, and marketing phenacetin (acetophenetidin) from a dye-making by-product. The company's switch from dyes to pharmaceuticals was so rapid that the first lots of the drug were alkylated in make-shift containers--empty beer bottles wrapped in towels--before the company decided to invest in suitable equipment and proper facilities for its production (6). However, despite the change in the products being manufactured, Bayer retained many of the methods used previously in the sale of dyestuffs in highly competitive markets: sales representatives, advertisements in trade journals, and the use of patents and trade names. As McTavish, a noted medical historian, remarks:

> By restricting its market to the pharmaceutical and medical professions, the chemical industry avoided the unseemly trappings of the nostrum trade and established itself as a member of the 'ethical' fraternity (7).

From then on, McTavish affirms, "[drug production] took place in an industrial setting. Drugs were commodities similar in most respects to any other commodity: they were manufactured for profit" (7). During the 1890's, Carl Duisberg and other key figures at Bayer were busily involved in reorganizing the company, in setting up pharmaceutical laboratories for the development and standardization of drugs, and, most importantly, in establishing links with the medical world.

The late nineteenth century saw an unprecedented rise in the number of new pharmaceutical products on the market. One physician in 1889 commented: "Every week, almost every day, brings its new drug, each in turn praised as being the greatest discovery of modern therapeutics" (8). McTavish attributes this tremendous influx of new products to "the increasing industrial role of the laboratory, especially in the drug industry" (7). However, the utility of these novel therapeutic products in medical practice was a source of great debate. Certain physicians staunchly opposed what they saw as "the growing tendency among German medical men to convert the 'Republic of Science' into a commercial oligarchy for the benefit of plutocrats at the expense of suffering humanity" (7). Others were more accepting of the new developments, but remained wary of those who hailed new compounds as milestone drugs or panaceas, "lest they bring into discredit both their own calling and that of the pharmaceutical chemist" (9). In an address on the Progress of Medicine in the Nineteenth Century, Dr. F. Roberts confessed:

> Out of the enormous number of medicinal agents brought under our notice by puffing advertisements in the press, medical as well as lay, by pamphlets or even large books delivered by post, or by actual 'specimens for trial' which are nowadays so liberally delivered at our residences, comparatively few hold their ground, or stand a fair and candid criticism and investigation of their vaunted merits. Still a certain proportion do and I see every reason to anticipate that, as the result of the systematic researches, scientific and practical, now carried on in so many laboratories, valuable additions will be made from time to time to the medicinal agents at our disposal for the help and comfort of our patients. I only hope that in our love for the new we will not entirely throw out old friends which have done real and effective service in the past and are today as deserving of our regard as ever (10).

Therefore, for those pharmaceutical companies that had managed to establish a place for themselves within the medical community, drug production became a legitimate science-based industry, whereby manufacturers and medics engaged in a profitable producer-consumer partnership. For instance, as written in the Lancet in August 1899, many new pharmaceuticals were the product of the increased attention paid "to the toleration of drugs and to the avoiding of effects which are undesirable" (11). Furthermore:

> Modification of the salicylates and the introduction of new morphine derivatives [which were both activities carried out in the Bayer laboratories] occur as single examples. In these matters it is satisfactory to find that the pharmacist is guided by the medical man and not solely by a knowledge of the chemistry of the principles concerned (11).

Thus, the inspiration and drive to produce aspirin can be explained in terms of a medico-industrial relationship in which the pharmaceutical companies supplied products that interested the doctors, and the doctors, in turn, maintained an active interest in what the pharmaceutical companies had to offer.

During the 1880s and 1890s, when physicians became intensely interested in the possible adverse effects of fever on the human body, the use of antipyretics became one of the hottest topics in therapeutic medicine. According to one pharmacology textbook published at the beginning of the 20th century:

> From the highest to the lowest in the profession, the fad was to regard fever as the most deleterious factor in a case, and to treat it as if it were a part of the disease, or the disease itself, instead of a symptom of almost all infections, and one which in itself is not capable of doing harm, unless it is excessive or very prolonged. [It was believed] that not only did fever, when sufficiently high, coagulate the protoplasm of vital parts, but that the patient was having his tissues burnt up, and that this excessive combustion, or conflagration, must be arrested even though the disease spent itself unaltered in its other clinical manifestations and pathological tendencies. The discovery by numerous laboratory investigations that this group of drugs decreased heat production, and increased heat dissipation, seemed to fit them in a peculiar manner to meet the therapeutic needs of the hour, and they were tested on a scale of experimental therapeutics hardly before equaled. At first, cases of untoward effects were frequently recorded, with fortunately very few fatal cases. Often these effects were due to heroic doses; in other cases, when patients in low fevers received the drug, the fall in temperature which succeeded produced collapse; while in maladies like pneumonia, with deficient aeration of the blood, or other pulmonary affectations, cyanosis, excessive sweating, and feebleness of the circulation occurred (12).

Therefore, until the fever fad ended at the turn of the century, most likely as a result of the increasing popularity of the germ theory, most physicians concentrated their efforts on treating pyrexia. The drug companies responded to the medical demands of the day by catering to, and perhaps even fueling the fires of, the antipyretic era. New antipyretics and analgesics--most drugs in this class were believed to possess more or less of both properties--were introduced monthly: "those coal-tar crystalline products which have almost deluged the market as quinine substitutes, [were] being offered from time to time as analgesics, anodynes, antipyretics, as the case may be" (13). Moreover, most of these new therapeutic compounds were commonly promoted as and subsequently referred to by catchy brand names such as malarin, pyrantin, cosaprin, phesin, eupyrine, and, of course, aspirin (14).

Still, it is not exactly clear how aspirin came to be. Many give the title of "discoverer of aspirin" to Felix Hoffmann, a chemist at Bayer whose father suffered from rheumatism. According to legend, Hoffmann's father was taking salicylic acid, already mass-produced, widely used, and highly profitable by the end of the 1870s, to treat his rheumatic condition. Unfortunately, the drug was terribly irritating to the stomach and was associated with other ill-effects: most notably, in addition to having an unpleasant, sometimes nauseating, taste, it was believed that salicylic acid disrupted digestion and had an enfeebling action on the heart (16,17). Therefore, the dutiful son took on the task of developing a less toxic replacement. However, acetylsalicylic acid (ASA)--the common chemical name of aspirin--may have already been produced by the French chemist Charles Frédéric Gerhardt in 1853, although he called his compound acetosalicylic anhydride, which was not necessarily the same as ASA. The compound was synthesized in a purer form by Johann Kraut in 1869. Indeed, acetylsalicylic acid was already being manufactured by the Chemische Fabrik von Heyden Company in 1897, although without a brand name. Therefore, it is difficult to determine whether Hoffmann truly developed a new chemical compound or even a novel method of producing a known one, which could then have been patented in Germany.

In addition to the uncertainties regarding the chemical origins of ASA, the prevailing medical opinions

concerning the widely-used salicylic acid and related compounds, including acetylsalicylic acid, were mixed. Similarly, there was a wide divergence in opinion within the Bayer pharmaceutical laboratories concerning the value of the work being done on ASA in 1897. According to Mann and Plummer, there was a certain degree of animosity between Arthur Eichengrün, who ran the research and development-based Pharmaceutical Division where Hoffmann worked, and Heinrich Dreser, who was in charge of testing and standardization in the Pharmacological Division (5). Eichengrün supported Hoffmann's chemical compound, whereas Dreser initially had no interest in even testing it as a potential new drug. Apparently, Eichengrün even went so far as to surreptitiously distribute the compound to physicians for trials. However, it was Dreser who eventually published the first article on aspirin. His change of heart regarding the value of this compound likely reflects his own financial interests, since, according to Mann and Plummer:

> [Hoffmann and Eichengrün] had contracts with Bayer by which they would receive a royalty on any patentable product they invented. Since there was no patent, neither of them received any royalties from the sale of aspirin in Germany. However, Heinrich Dreser had an agreement with Bayer by which he would receive a royalty on any product that he introduced. Thus he received a very substantial royalty for aspirin and was able to retire early a very rich man (5).

As suggested in the July 1899 issue of the Lancet:

> No one [in the pharmaceutical industry] would undertake the irksome task of making new products known to the medical profession without being, whether rightly or wrongly, convinced of their superior properties (17).

Therefore, once Dreser finally chose to promote Hoffmann's chemical compound as aspirin, he certainly built up a strong case for its superiority over other available remedies.

In his article published in the *Archiv fur die Gesamte Physiologie* in 1899, Dreser begins by describing the unsatisfactory nature of the drugs then available, thereby creating the need for new alternatives:

> In many diseases related to common cold, the use of sodium salicylate would be definitely much more popular if it would not provoke strong rejection by its disgusting sweet taste which can be corrected only to some extent (18).

Dreser then suggests:

> Pharmacological chemistry should develop synthetically a new preparation which would avoid in addition to the disgusting sweet taste other undesirable characteristics such as the overloading of the stomach. After resorption, the active salicylate should be rapidly split off from the new product.

These improvements are precisely what Dreser claims to have achieved through the synthesis of aspirin. First, the taste was refined by masking the free phenolic hydroxyl group of salicylic acid through substitution of the hydrogen atom with a methyl group. To prove that aspirin is reabsorbed and cleaved into salicylic acid, Dreser cites the work of the German scientist Lesnik published in the *Archiv fur Experimentelle Pathologie und Pharmakologie* to maintain that the increase of nitrogen in the urine "could be due only to the nitrogen-containing metabolic product of salicylic acid . . . also clearly shown by aspirin."

Dreser then carried out comparative studies of aspirin and other salicylates to demonstrate that the former was less noxious and more beneficial than the latter. For instance, he tested the sodium salt of aspirin and sodium salicylate on normal rabbits and on cold-blooded animals, which, to his mind, "showed clearly that aspirin is less poisonous than salicylic acid." Dreser also tested aspirin on the most fine and delicate tissues, such as the gills of fish, to further demonstrate the gentleness of the compound. Finally, to put to rest any

fears that aspirin might depress the heart, he conducted experiments to show that sodium salicylate decreased cardiac output, whereas the sodium salt of aspirin increased it. Dreser concludes his article as follows:

> Summing up the most important pharmacologic characteristics of aspirin we may suggest the following: The aspirin has a more pleasant harsh acidic taste than sodium salicylate before resorption. It is also more protective to the stomach wall according to the above experiments. It is very advantageous, furthermore, that aspirin is split by the gastric hydrochloric acid only to a small extent (0.2%). Differences are evident between aspirin and sodium salicylate also after resorption... (18).

By publishing these findings in a physiological journal, Dreser was able to provide a "scientific" and "objective" account of this new compound as a potentially powerful pharmaceutical product with few side-effects. At the same time, he was one of the top employees at Bayer, and would therefore benefit personally from the success that his pharmacological analysis had brought upon aspirin.

In concert with Dreser's efforts, physicians were co-opted into supporting the effectiveness and harmlessness of aspirin. Two such doctors cited in Dreser's article were Dr. C. Witthauer, who published a paper on his experiences with aspirin in *Die Heilkunde* in April 1899, and Dr. Julius Wohlgemuth, who had his results published in *Therapeutische Monatshefte* in May of the same year. Both Witthauer's and Wohlgemuth's articles (19,20) provide a general introduction to the novel powder, corroborate Dreser's findings, and describe the results of clinical trials with aspirin. Unequivocally, they conclude that the new drug is superior to the other pharmaceutical products then available.

The elegance of the early medical and pharmaceutical reports lies in their ability to ally aspirin with the already widely accepted salicylic compounds, whilst concurrently presenting aspirin as distinct from them. Thus, the new drug possessed a certain familiarity, and more importantly, the manufacturers could then claim the proven medicinal properties of salicylic acid and related compounds by association. However, it was equally important to disassociate aspirin from the negative qualities that had been attributed to these products through the development of scientific truths in the laboratory which attested to such differences. In this way, a white powder that had spent many years collecting dust on a shelf along with hundreds of other chemical compounds stored at Bayer was transformed into a substantive pharmaceutical product. Since then, each new report by members of the medical community or pharmaceutical world has expanded and altered the ever-growing narrative on aspirin.

On July 22, 1899, aspirin was featured in the "Analytical Records from the Lancet Laboratory" along with several other products that had undergone the rigors of scientific analysis: an old pale cognac found to be suitable for medicinal purposes; Johannis potash water, a diuretic and alkaline treatment; Sandron's iron tonic, which was found to contain a very small quantity of iron; and finally, two specimens of Scotch whisky. The journal's announcement of The Bayer Company's latest drug resembled, in both content and intent, the articles published previously by Dreser, Witthauer, and Wohlgemuth. Within a few years, a barrage of articles singing the praises of aspirin had been published. The clinician Floeckinger even went so far as to take two large doses of aspirin himself: first 75 grains and then another 60 grains (21). After the first dose he found himself "without toxic effects, except violent headache and tinnitus" which lasted for 16 hours, until it subsided following profuse sweats. After the second dose, Floeckinger experienced "increased pulse, reduced temperature, and flashes of light before the eyes." Nonetheless, Floeckinger concludes his article as follows:

> [It] presents several advantages over salicylic acid. It does not irritate the stomach. There is no cardiac depression. In ordinary doses there is no tinnitus or headache...and [it] is best prescribed in wafers or sachets for acute and chronic rheumatism, polyarthritis, and pleurisy...but it is ineffective in neuralgias and pleurodynia (21).

Any adverse effects experienced when taking aspirin were attributed not to this new drug, but rather to extrinsic factors, such as the medium of administration or the magnitude of the dose. Although certain physicians claimed that "some observers--Osler, for instance--recognize little or no advantage in salicylates beyond some power in relieving pain" (15), most physicians strongly supported aspirin as a valuable addition to the pharmacopoeia.

Soon after its release onto the market, aspirin began to appear in the new pharmacological texts. Nonetheless, there were still many recent and reputable works that did not mention Bayer's new drug (12,22,23). Indeed, even when aspirin was included in these works, it was not always cited for use in treating ailments with which one now associate the drug. The Index of Diseases and Remedies in an American textbook on materia medica, pharmacology and therapeutics, for example, cites aspirin for the treatment of certain diseases, but does not prescribe it as a general substitute for salicylic acid and the other salicylates. The text lists salicylic acid as a drug useful for burns, eczema, ephelides (freckles), lupus vulgaris, pertussis, and ulceration. Salicilin, salol, salipyrin, and other salicylates are recommended for different disorders such as chorea, diabetes mellitus, endocarditis, fever, pharyngitis, and pleurisy, whereas aspirin is recommended, in addition to other drugs, in the treatment of influenza, neuralgia, and neuritis (24).

Indeed, within the first five years after its release, aspirin was seen less and less as an antipyretic, and was increasingly prescribed for the relief of pain. By 1903, "numerous observations had been made on the analgesic effect of aspirin in neuralgias and other painful affectations," including carcinoma (25). In this way, aspirin was similar to its predecessor phenacetin, which "found its birth in what may be called the antipyretic era [of the 1880s and 1890s, and] like its relatives has come to be employed chiefly for the relief of pain" (12). The shift in interest from the antipyretic to the analgesic properties of these drugs in the early twentieth century is best summarized by the entry in the *Text-book of Pharmacology and Therapeutics* of 1901:

> As the fad for antipyresis waned by its loss of novelty, physicians began to ask each other whether these drugs which acted so well in reducing fever had any influence in shortening the course of the disease, and it was speedily determined that they did not. Simultaneously, the increasingly thorough investigations into the pathology of fever, and our increased knowledge of the life history of the organisms causing disease, made it clear that fever was a comparatively unimportant factor in a given case, unless excessive; and it begins to be apparent that fever is not only not a peculiarly harmful process, but in some cases may be actually of value... Finally, the recollection of the fact that the use of these drugs necessitates their absorption and elimination, changed or unchanged, and that in these processes they may be guilty of a deleterious influence, has still further decreased their popularity as antipyretics, while the discovery that all of them possess pain-relieving properties has also diverted attention to their use for other purposes than antipyresis (12).

Thus, the uses of aspirin changed with the changing trends in the medical profession, becoming progressively less linked to the drug's initial description and indications first marketed by the pharmaceutical company. The original experiments conducted on aspirin in the Bayer laboratory were superceded by more recent clinical findings conducted by medical men not affiliated with the pharmaceutical company. Gradually, all the stories told by those who had been instrumental in presenting and promoting acetylsalicylic acid as aspirin faded into the background. By 1903, authors no longer felt the need to include comprehensive profiles of aspirin in their articles: "the remedy is now sufficiently known to make its description unnecessary here" (15). Thus, the original narrative of aspirin had been disseminated and accepted by the medical profession to such an extent that it no longer needed repeating.

Aspirin had quickly become a household name around the world, finding its way even into literary works of the early twentieth century. For instance, when the young Lady Caroline Desta of Elizabeth von Arnim's 1922 novel *The Enchanted April* complained of a headache during a holiday in Italy, one of her companions asked,

"Do you know what aspirin is in Italian?"--to which an erudite old Englishwoman interjected that "the proper remedy for headaches...is castor oil." In a similar vein, Franz Kafka once explained to his fiancée Felice Bauer, in the course of their tormented relationship, that aspirin was one of the few things that eased the unbearable pain of being (5).

Aspirin has certainly been put to many different uses throughout the twentieth century, and serves as an example of one of many products of the novel and tenuous relationship that developed during the late nineteenth century between laboratory science, the manufacturing industry, and medical humanitarianism. Indeed, the early pharmaceutical industry's establishment of a close association with the medical community and its adoption of scientific techniques, or, at the very least, a scientific veneer, were instrumental in its success, "and changed the character of medical practice as much as it did the industry itself" (26). Over the years, these medico-industrial connections have consolidated to form the modern pharmaceutical industry of today, an industry that has pervaded almost all aspects of medical science and practice.

The story of aspirin--its origins, popularization, and varied uses--is rather unique:

> Few groups of drugs have provided the manufacturers with such fortunes, physicians with such therapeutic resources, and the laity with so many semi-proprietary remedies as have the so-called antipyretic or analgesic derivatives of coal tar. Nor is there any group which illustrates so well the close relationship between chemistry and practical therapeutics, and the relation of chemical constitution to physiological action (12).

Yet, the story of aspirin to a great degree epitomizes the stories of many pharmaceutical products developed both for increased therapeutic efficacy and for profit. The histories of these products generally share certain themes. The usually vague and contentious origins of a drug soon become overshadowed by the multitude of clinical reports produced with the help of medical allies. Extensive clinical trials serve to introduce new drugs to the greater medical community, to specific patient groups, and eventually, to the population at large. As the years pass, however, many drugs are used to treat diseases different from those for which the drugs were originally intended. For example, with the advent of the "anti-coagulant era," aspirin has acquired new indications as a platelet anti-aggregant, and is already widely used in the prophylaxis and treatment of strokes and myocardial infarcts. Therefore, drugs currently being produced and prescribed remain a reflection of the ever-changing state of medical knowledge and of the pharmaceutical industry's eagerness to meet the needs of the day.

As the quest for more potent and less toxic drugs continues in the age of rational therapeutics, advanced technology, and designer drugs, the treatment of disease continues to be shaped by the symbiotic relationship between physicians and pharmaceutical companies forged a century ago.

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