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HOT TOPICS IN PAIN AND HEADACHE (N. ROSEN, SECTION EDITOR)

History of NSAID Use in the Treatment of Headaches Pre and Post-industrial Revolution in the United States: the Rise and Fall of Antipyrine, Salicylic Acid, and Acetanilide

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Abstract
Purpose of Review Non-steroid anti-inflammatory drugs (NSAIDs) constitute a vital class of medications in today's headache regimen. However, up until the nineteenth century, they were largely unknown to most of the medical community. The purpose of this review is to explore the evolution of NSAIDs in the treatment of headaches spurred on by the Industrial Revolution in the USA.
Recent Findings The currently available data on the impact of NSAIDs reflects their significant contribution to headache treatment.
Summary The emergence of mass production spurred on by the Industrial Revolution, lead to widespread use of antipyrine, salicylic acid, and acetanilide. However, along with it came the growing awareness of consumer safety, leading to their ultimate downfall, and the subsequent birth of the Food and Drug Act.

Keywords Headache · NSAID · History · Antipyrine · Salicylic acid · Acetanilide · Post-Industrial Revolution

Introduction

Over the course of the nineteenth century, there was a dramatic evolution in headache management spurred on by the Industrial Revolution in the United States. Though the theories regarding headache mechanism held firm, the surge in mass production and capitalism stimulated a new medical milieu. Not only was there an evolution in the producer-consumer relationship, but the large market of new medications spurred on the growing popularity of evolving group of non-steroidal anti-inflammatory drugs, dramatically changing the tide of headache management nationwide. It was at this time that salicylic acid, antipyrine, and acetanilide made their introduction. Though quickly becoming household names at the time, the history of their creation, rise in popularity, and ultimate downfall is unknown to most.

Topical Collection on *Hot Topics in Pain and Headache*

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Pre-Industrial Revolution Headache Theory and Remedy

Similar to the times of Galen or Hippocrates, in the mid 1800s, society endorsed a holistic, humoral view of medicine in which headaches were viewed as a symptom of some deeper derangement of its constitution but never a disease in itself. It had many manifestations and triggers which made it a challenging conundrum. The goal of therapy was to get rid of the cause of pain rather than the pain itself. Therefore, physicians were not inclined to use analgesics such as opiates to treat it. That does not mean that headaches were left unaddressed, but merely that the public was often left to find their own means of relieving their pain and there were many home remedies for it.

Home remedies for headaches were numerous and differed based on regional or ethnic beliefs and humoral precepts. Some techniques were based on magical principals such as transferring suffering to another creature. In North Carolina for example, it was believed that someone who had squeezed a mole to death was able to cure headache by touching the affected area with the hand which performed the action [1]. More prevalent was the belief that headaches were caused by the evil eye and could be prevented by prayers, incantations, and amulets. Some remedies were based on the principal that ill health was due to the accumulations of toxins in the body and the remedy was removing them from the body. Some used

leeches at the onset of headaches applying them to the temples and behind the ears to stop further progression in severity [2]. Others found toxins in the gastrointestinal tract to be the culprit and used purges, vomiting, and sodium bicarbonate for better regulation. Diaphoretics, which induced sweating, and sialogogues, which induced salivation are also means of purifying the body of headache-inducing elements. More practical methods were using cloth dampened by water, lavender, or peppermint, comfrey [3••]. Others, if fortunate enough, were recommended champagne to soothe their nerves [3••].

Other oral remedies included multiple concoctions of berries, bards, roots, and leaves to form teas. Therefore, there was no dearth of possible remedies one could try to at home for headaches.

Only when such home remedies failed and headaches were severe did the public turn to physicians for relief. However, professional assistance was no less complicated as there was no shortage in the theories and therapeutics offered by physicians in the nineteenth century. Overall, physicians also viewed headaches and all illnesses as being a manifestation of systemic imbalance either with itself or its environment [4]. Often, they were held in high prestige for their dedication to medical knowledge and unique skills in identifying the source of imbalance. For that, physicians heavily depended on keen observations of physical derangements and complaints such as dizziness or double vision that accompanied complaints of headache. Once found out, it followed that one could restore equilibrium by counteracting the deficient or excessive element. This was often accomplished by stimulation (i.e., of appetite) or sedation; revulsion, which diverted the pathology to another part of the body; and supersession, which replaced one disease with another [5]. Often, this resulted in the use of cathartics, diaphoretics, emetics, or a complicated concoction of ingredients written in Latin which sanctified physicians' special knowledge.

Industrial Revolution and the Rise of New Medications and Marketing

With the rise of the Industrial Revolution in the nineteenth century, the supply of medications and herbs for headaches dramatically increased. There was a transition to new manufacturing which consisted of going from hand production methods to machines, new chemical manufacturing and production processes, more efficacious means of water power, and the rise of steam power. Trade flourished and towns were full of large wholesale retailers of local and imported raw goods. Local firms produced alkaloids, such as quinine, strychnine and morphine serving physicians and local apothecaries. There were specialty manufacturers and importers as well who provided goods that were not otherwise available locally.

Despite the potentially dangerous nature of many of their products, there were no state or federal laws in the nineteenth century that required customers to have professional credentials. As doctors were often of limited supply, Americans were entitled to doctor themselves and buy without limitation [6]. If customers poisoned themselves, it would only be the fault of the supplier if the item was adulterated or incorrectly labeled [7]. As their target market was unrestricted, suppliers focused much effort on marketing to ordinary citizens and domestic practitioners. Newspapers were replete with local druggists' advertisements listing their products and those of their suppliers. Catalogs, such as those provided by the George B. Carpenter Company of Philadelphia, contained lists of medications, raw chemicals, and even surgical supplies. Chests of essential drugs labeled in Latin or English were readily available for consumer purchase, conveniently packaged with measuring spoons and flasks; Carpenter's own Dispensatory, which listed "the properties and doses of each article most approved in Domestic Medicines"; and a "concise Description of Diseases with directions for the treatment of such as are unattended with serious consequences, shewing also the best immediate measures to be adopted in those disorders and accidents which are destructive to life, when the physician is not at hand or until his assistance can be procured" [8].

In the 1840s, a Massachusetts shoemaker introduced a new concept to American medicine. His name was Perry Davis and he had grown increasingly frustrated with existing remedies for his chronic pain. Therefore, he made his own and it worked so well he decided to market it to the rest of the world as Davis' Painkiller. It was the first product marketed as an analgesic. In fact, it was a word that he made up himself, which he registered as part of a trade name, with the recipe kept secret. It was the forefather of patent analgesics in the America [9].

Patented medicines were not unfamiliar in America. They had originated in Europe in the 17th and 18th centuries as mass produced and mass advertised variations of complex prescriptions. Brought over to the New World by colonist generations prior Americans were willing to consume what relief was available when unable to consult a physician. Though familiar as it was, patent medicines were not entirely respectable in America because they appeared to prostitute medical wisdom for personal gain [3••]. Until the nineteenth century, drugs were produced and marketed largely motivated by idealism more than profits. Public opinion was that businesses were run by believers in health reform who would take advantage of medical review publications to voice opinions on new medical recipes which were usually freely listed [3••]. However, after the arrival of Perry Davis' Painkiller, many questionable remedies were being marketed. Often they were sold by unassuming suppliers and physicians who were wooed by false marketing. The potential for capitalistic success was unbridled in light of lavish advertising and no regulations restricting what the recipe contained and the claims that could be made about it. In fact,

so broad were the services offered by these drugs that historians have commented that patent medicine makers were the first merchants to recognize that they were not filling a need so much as creating one. For example, manufacturers "first had to sell them a sense of themselves as diseased" [10]. This often took the form of public attacks on halitosis, body odor, acne, dyspepsia, and rheumatism. Furthermore, tradition held that left unaddressed, these minor deficits and pains had the potential of becoming significant ones. It has been proposed that in order to generate sales, medicine vendors often took advantage of the population's fears by inventing or exaggerating dangers of such symptoms. If nothing else, the success of Perry Davis and those who trailed behind him was a testament that Americans were no longer willing to tolerate pain and were open to no longer just using natural remedies but whatever chemical concoctions manufacturers were able to provide.

Despite the bevy of remedies manufacturers had to offer, there was no one certain remedy for headache sufferers in the nineteenth century. Even those which contained alcohol provided comfort to only those patients who were able to bare the taste and the increasing amounts that were necessary to numb the pain. Even then, small amounts alone often exacerbated headaches for many. Opiates were also considered for severe headaches but often were tempered by the side effect of severe lethargy and addiction. Narcotics, typically laudanum, an ethanol extract of crude opium, were available but were unpopular because of side effects such as sleepiness, constipation, and the risk of addiction. Quinine, a coal tar byproduct, had been used in the West since 1640 to treat the high temperature, fever, and headache caused by malaria. In 1842, Charles Gerhardt introduced an inexpensive derivative of quinine, called quinoline, as a treatment for typhoid fever, acute rheumatism, neuralgia, head, and facial pain [11•]. However, in a few individuals, quinoline caused cyanosis, a bluish coloration of the skin brought on by an inadequate supply of oxygen and often associated with heart disease. Its partially hydrogenated derivative, kairine, introduced in 1882, also caused cyanosis for some patients. So, in the second half of the nineteenth century, there was a need for more acceptable analgesics for everyday use. It was at that time, the industrial revolution fueled the development of several early synthesized anti-inflammatories.

The Introduction of NSAIDS in Headache Treatment During the Industrial Revolution

Salicylic Acid

The medicinal value of salicylic acid has long been venerated by cultures throughout history. Stone tablets from the Sumerian period describe the use of willow leaves by Assyrian physicians to treat inflammatory rheumatic conditions is the first of such documented uses [12]. Likewise, willow bark was referenced later by European scholars during time of Hippocrates. Henceforth, these scientific inquiries evolved in 1763 with the publication of a letter in 1763 from Reverend Edward Stone touting its benefits in the treatment of agues, the term then used for malaria [13]. Many chemical and clinical trials were initiated throughout Europe thereafter. However, up until 1859, salicylic acid was available only as a derivative from willow bark. Through the work of the German chemistry professor, time of Hermann Kolbe, it became possible to produce salicylic acid on an industrial scale for one-tenth of the cost of extracting the compound from willow bark [12]. It gained widespread popularity in the commercial market for numerous inflammatory conditions including rheumatic fever, rheumatoid arthritis, gout, and headache. Unfortunately, its popularity was limited by its unpleasant side effects, namely gastric irritation and unpleasant taste.

Its further development into the well-tolerated and still widely used acetyl derivative, aspirin, did not occur until the late 1880s in Germany. The advent of aspirin had long been attributed to young chemist, Felix Hoffman, then employed at dye manufacturing company, Farbenfabriken Bayer, also known as Friedrich Bayer. Hoffman had a personal motivation to make salicylic acid more palatable as his father had long suffered from arthritis [14]. However, the heritage of Aspirin had recently come into question by Dr. Walter Sneader of Stathclyde University (Glasgow, UK) [15]. He had become suspicious of said history when researching for a lecture on aspirin and requested the Bayer Company to allow him to examine Dr. Hoffman's notebooks. Upon doing so, he found that Dr. Hoffman's supervisor, Dr. Arthur Eichengun may have been the originator. Though Hoffman did undoubtedly synthesize aspirin in 1897, it was clear from Dr. Sneader's investigations that Hoffman had methodically adapted Eichengrun's scheme to make salicylic acid more tolerable [16]. In 1934, Hoffman claimed the work as being solely of his own initiative. Per Dr. Sneader's investigations, due to anti-semitic sentiments of the 1920s and 1930s, it was difficult to repute the chronology of events reported by Hoffman. However, later in 1948, Eichengrun published his version of the events in an article in Die Pharmazir 1 month before his death [15].

It is said that the name was derived by the director of research at Bayer at the time, Henrich Dresler. He noted the challenge in pronouncing the name acetylsalicylic acid, and the very close resemblance to the predecessor salicylic acid, therefore sought a new simple name. He recalled the natural salicylic acid had been prepared from plants of the Spiraea family, and so "A" was added for the acetyl to "Spirin" from Spiraea" to make Aspirin. Another theory is the name may have also sprung from the early Neapolitan Bishop, St. Asprinius, the patron saint of headaches [17]. Ultimately, in 1899, Aspirin thereafter had a patent protected name with complete monopoly for 17 years.

Interestingly, there had been many early attempts in the USA to wrestle the chemical industry away from the European monopoly at the time, but Aspirin became the means of doing so. In

1901, John Queeny, founder of the American Monsanto Chemical Works company, initially saccharin producer, became interested in manufacturing aspirin being spurred on by the impeding World War I [18]. In 1912, he sent an envoy, chemist Dr. Gaston Dubois, visited an unnamed chemist at Brugg in Switzerland and purchased a one-step aspirin production operation for 2000 Swiss Francs. This allowed the Monsanto Company to take lead in cheaply manufacturing large quantities of aspirin. In fact, Monsanto built a process plant in 1916 and by 1917 had sold 2368 lb of aspirin. Sensing the threat, Bayer of Germany battled for protection of their patent. However, in 1918, the US Patent Office cancelled Bayer's registered rights to the name, because they were thought to have been improperly registered. Furthermore, the US Supreme Court ruled that Bayer's aspirin had been over-advertised to such an extent that it had become a common name. After Germany lost World War I, Bayer was forced to give up the trademark as part of the Treaty of Versailles in 1919 [19].

Antipyrine

In 1883, Emil Fischer serendipitously discovered phenyl hydrazine. It was initially proposed that this compound would be an antipyretic and analgesic due to its close structural relationship to quinolone. However, upon further pharmacological analysis by his assistant, Ludwig Knorr, this was found not to be the case. Instead, he suggested alkylating the NH group, such that it would more closely resemble karine. This modification resulted in success that, "riveted the attention of the most prominent German physicians during the past summer" [20]. Noted to be safer than many other antipyretics at the time, including cold water, it had "received the endorsement of and is used by the leading practitioners in this country and abroad, and also in all the hospitals of this city" [21].

American doctor, John Blake White was among the first to discover that "fifteen grains of Antipyrine given in a single dose promptly relieves the symptom of headache whenever present, whether resulting from disordered digestion, disturbances of the menstrual functions, loss of sleep, undue mental effort, or even that associated with dreaded uraemia" [22]. He also found that patient could take it prophylactically to prevent "recurrent attacks of cranial neuralgia". Another physician stated in 1885 that he had prescribed Antipyrine in 18 cases of severe headache, migraine, or facial neuralgia, with only one failure [23]. Four patients with migraine told him that Antipyrine "acted like magic" and they had "never had anything so good". For five cases for which other than Antipyrine had been used, he stated, "antipyrin would have saved my patients much mental worry, and often the keenest physical suffering" [23]. It was found to be effective as an abortive treatment as well, with a Rhode Island physician at the time reporting for his own headaches that "almost immediately" after ten grains "the paroxysms was lessened, and within an hour or two there was complete relief", and subsequent migraines would occur less frequently and with lesser severity [3••]. Practitioners also noted that it was not unpalatable, sedating, habit-forming, nor noxious to the stomach as opiates.

Though selling at $1.25 oz, at almost twice the cost of quinine, antipyrine was used in much smaller doses, therefore more economical. Therefore in USA, its use was so widespread that it had become scarce, "the manufacturers in Germany were not being able to supply demand" [24]. It was even documented by medical author Walter Sneader in its use in the European influenza epidemic. For the next 15–20 years, Antipyrin was the most widely used drug in the world. The company Hoechst Dyeworks was producing upwards of 17,000 kg annually [11•]. Despite its immense benefit, the risks of Antipyrin did not go without notice. It caused in some people agranulocytosis, leaving patients vulnerable to infection.

Acetanilide

In 1886, acetanilide was the first aniline derivative serendipitously found to possess analgesic as well as antipyretic properties. At the University of Strassburg, Professor Adolf Kussmaul had been testing multiple agents, including a coal tar product by the name of naphthalene, for the treatment of intestinal worms. When his two assistants Arnold Cahn and Paul Hepp, used naphthalene for a patient suffering from a multitude of complaints in addition to worms, they observed an antipyretic effect [25]. However, further investigation revealed that the pharmacy had supplied not naphthalene, but acetanilide, which was a nearly identical appearing crystalline substance. Acetanilide was marketed under the name Antifebrin, registered to Kalle and Company. It quickly gained popularity as an antipyretic because it was not only effective, but remarkably inexpensive. Compared to antipyrine at $1.25 an ounce, antifebrin was sold at only 25 cents [26]. The reasoning behind such a price was the fact that unlike its competitors, it did not possess a US patent. Furthermore, with the name Antifebrin, it held a commercial appeal that propelled its widespread use as antipyretic. Antifebrin was eventually replaced by other safer analogs, notably phenacetin, first synthesized in 1887.

Samuel Hopkins Adams' articles in Collier's were particularly scathing. "Acetanilide will undoubtedly relieve headache of certain kinds; but acetanilide, as the basis of headache powders, is prone to remove the cause of the symptoms permanently by putting a complete stop to the heart action. Invariably when taken steadily, it produces constitutional disturbances of insidious development which results fatally if the drug be not discontinued, and often it enslaves the devotee to its use." In "The Subtle Poisons" he listed 22 Americans alleged to have died because of taking acetanilide in headache remedies, not including "…the dog in Altoona, Pa, which died immediately on eating some sample headache powders. The dog did not know any better." Another article called out

acetanilide as being "…so dangerous that even the most skillful physicians nowadays are refusing to prescribe it" [27].

Phenacetin

Encouraged by the success of acetanilide, young research chemist Carl Duisberg, sought a way to further diversify the commercial interests of Bayer. In particular, he was looking to making use of the over 30,000 kg of paranitrophenol being stored as waste and to find a use for 4-nitrophenol, a side product available in vast amounts from its synthesis of the blue dye [11•]. Duisberg, challenged his team members to come up with an exploitable use for this compound. One of them, Oscar Hinsberg, found that in three steps—i.e., reduction of NO_2 to NH_2; ethylation of the OH group; and finally acylation of the NH2group—he had made a well-tolerated antipyretic and analgesic. In clinical trials, it demonstrated all the advantages of Antipyrin and Antifebrin and (apparently) none of their disadvantages. His new product, phenacetin, enjoyed much popularity for almost a century as an over-the-counter remedy (often combined in tablets with caffeine and aspirin) for headaches and hangovers. It is also known historically to be one of the first non-opioid analgesics without anti-inflammatory properties. Despite its initial success, Bayer was not able to ensure exclusive property of the trade name Phenacetin. By the mid 1890s German courts had determined that the name Phenacetin was a generic word, although the company was able to successfully prosecute others for trademark infringement outside of the country. However, in the 1960s, evidence was mounting to suggest that phenacetin might be causing renal failure and renal tumors in some heavy users. In addition, people with glucose-6-phosphate dehydrogenase deficiency may experience acute hemolysis. In 1980, phenacetin was banned in the UK, later in USA, and still produced in some parts of the world, including India.

Drug Regulation

Jobbers solicited customers from all walks of life. Physicians at the time were not opposed to open access as their presence was of short supply. Therefore, oftentimes the public was left to a degree of self-care. Medicine was one of the first markets that used nationwide advertising, with catalogs containing a wide array of drugs and chemicals with sales pitched geared to doctors, chemists, shopkeepers, and locals. Suddenly the trickle of sham medications which had always managed to exist flooded the marketplace as tradesmen and corporations saw the possibilities for profit. New patent medicines consisted of ingredients disclosed to neither the doctors who administered the "drugs" nor the patients who took them. This fostered an environment of unbridled capitalism and risk to the public. Despite the drugs and raw goods being for specialized uses with potentially deadly consequences, there was virtually no state or federal law mandating medical or other professional licensing before having goods shipped to them.

Rising public concern prompted the movement of national drug regulation in the mid 1800s with the advent of the Drug Importation Act passed in 1848 by Congress which required U.S. Customs Service inspection to stop entry of adulterated drugs from abroad. A prominent historian at the time, Gordon Wood, recalled, "It was frightening and bewildering to many-that a whole society should be taken over by moneymaking and the pursuit of individual interest". President Abraham Lincoln viewed corporations as the new class of tyrants to replace those dethroned less a century before. "Corporations have been enthroned," Lincoln said. "An era of corruption in high places will follow and the money power will endeavor to prolong its reign by working the prejudices of the people … until wealth is aggregated in a few hands … and the Republic is destroyed." The time "brought forth many changes in business life and left many evils that called to high heaven for remedy."

In 1862, President Lincoln appointed chemist, Charles M. Wetherill, to serve in the new Department of Agriculture. This was also the beginning of the Bureau of Chemistry, the predecessor of the Food and Drug Administration. In 1880, Peter Collier, chief chemist, U.S. Department of Agriculture, recommended passage of a national food and drug law, following his own food adulteration investigations. The bill was defeated, however, during the next 25 years, over 100 food and drug bills were introduced to Congress. In 1883, Dr. Harvey W. Wiley became chief chemist, expanding the Bureau of Chemistry's food adulteration studies. Wiley and his team revealed the existence and negative health repercussions of a multitude of chemical-cheapening ingredients, colorings, and preservatives being surreptitiously used to change the appearance, smell, and taste of bad foods and drugs. Honoring this passionate commitment and campaign for a federal law, Dr. Wiley is called the "Crusading Chemist" and "Father of the Pure Food and Drugs Act." His long struggle eventually paid off in 1906 with the passage in Congress of the original Food and Drugs Act on June 30, 1906 signed by President Theodore Roosevelt. The Food and Drug Act was a legal proclamation with the aim of "…preventing the manufacture, sale or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein, and for other purposes" [28]. Around the same time, "The Harmfulness of Headache Treatments" was also released, which led to the publication and eventual disuse of acetanilide and related medications. Thus, with the extinction of the old, there was room for other new NSAIDs such as ibuprofen and naproxen.

Conclusion

Thus, over the course of the nineteenth century, the USA went through a drastic change in their medical approach to headache

management. With the advent of mass production, small-town alchemists were quickly replaced by industry backed chemists. This new form of commercialism became a boon, especially in areas of scarcity. However, at the same time, society was being supplied with a greater variety of unregulated medicines, often resulting in deleterious consequences that went unchecked. It was in this medical milieu that the first generation of NSAIDs, antipyrine, salicylic acid, and acetanilide, was born. Stirred by growing unease with lack of consumer protection and commercial greed, evidence-based medicine and federal regulation slowly took shape and resulted in the Food and Drug Act. Therefore, the same forces that uprooted traditional humoral medicine and introduced NSAIDs, led to eventual weeding out of not only dubious trade practices, but also to the extinction of antipyrine, salicylic acid, and acetanilide as well, henceforth making room for the next generation.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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