Salicylates and Pandemic Influenza Mortality, 1918–1919 Pharmacology, Pathology, and Historic Evidence

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The high case-fatality rate—especially among young adults—during the 1918–1919 influenza pandemic is incompletely understood. Although late deaths showed bacterial pneumonia, early deaths exhibited extremely "wet," sometimes hemorrhagic lungs. The hypothesis presented herein is that aspirin contributed to the incidence and severity of viral pathology, bacterial infection, and death, because physicians of the day were unaware that the regimens (8.0–31.2 g per day) produce levels associated with hyperventilation and pulmonary edema in 33% and 3% of recipients, respectively. Recently, pulmonary edema was found at autopsy in 46% of 26 salicylate-intoxicated adults. Experimentally, salicylates increase lung fluid and protein levels and impair mucociliary clearance. In 1918, the US Surgeon General, the US Navy, and the *Journal of the American Medical Association* recommended use of aspirin just *before* the October death spike. If these recommendations were followed, and if pulmonary edema occurred in 3% of persons, a significant proportion of the deaths may be attributable to aspirin.

> In February 1919…Edward's fever kept getting higher and higher…aspirin…was given to him by the 1/2-handful over and over…Edward sweated through his mattress…Dr.…could not save his patient.
>
> —Clella B. Gregory, Pandemic Influenza Storybook, US Department of Health and Human Services [1]

The unprecedented overall mortality and the mortality rate among young adults during the 1918–1919 influenza pandemic are incompletely understood. Deaths in the United States peaked with a sudden spike in October 1918. Later, Wade Hampton Frost [2] studied surveys of 8 US cities and found that, for every 1000 persons aged 25–29 years, ~30% were infected with influenza virus, and 1% died of pneumonia or influenza. This 3% case-fatality rate has been called, "perhaps the most important unsolved mystery of the pandemic" [3, p 1022].

Mortality was driven by 2 overlapping clinical-pathologic syndromes: an early, severe acute respiratory distress (ARDS)–like condition, which was estimated to have caused 10%–15% of deaths (sequential autopsy series are lacking) [3)]; and a subsequent, aggressive bacterial pneumonia "superinfection," which was present in the majority of deaths [4, 5].

Factors that contributed to the severity of illness and death (eg, viral pathogenicity, bacterial colonization, immune response, smoking, preexisting conditions, and treatment) remain to be elucidated. Of most interest are

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those amenable to intervention, because fear of another 1918-like influenza pandemic drives pandemic planning today.

Recent studies suggest enhanced pathogenicity of certain influenza viruses as well as abnormal immune host responses. The 1918 influenza H1N1 virus, in contrast to a conventional human H1N1 influenza virus (A/Kawasaki/173/01), infected the lower respiratory tract, produced acute respiratory distress, and was associated with a dysregulated antiviral response in a cynomologous macaque model [6]. Also, the 1918 viral polymerase complex (PA, PB1, and PB2) promoted growth of the 1918 virus in the lower respiratory tract of ferrets [7]. Similarly, 2003 human H5N1 isolates, like 1997 human H5N1 isolates, induced overproduction of proinflammatory cytokines in human macrophages in vitro [8].

However, it is unlikely that the virus and immune responses alone were responsible for the 1918 deaths. As recently reviewed by Brundage and Shanks [4], most persons had self-limited disease with case-fatality rates of <2%, and mortality and case-fatality rates differed widely among populations. During the fall of 1918, death and influenza case-fatality rates ranged from 0.58% to 3.3% and 2.1% to 10%, respectively, in the 12 US Army camps with >10,000 cases of influenza or pneumonia each [9, 10]. Frost [2] noted that the wide variation in mortality rates between cities, some of which were close together, was not explained by climate, population density, preventive measures, or other environmental characteristics. These observations suggest the importance of factors related to location rather than the virus itself. Likewise, the unusual mortality rate among young adults remains unexplained. Salicylate has been suggested [3, 11, 12], and increased mortality rates have been found in ferrets exposed to influenza, aspirin, and an arginine-deficient diet, compared with each alone or in 2 combinations [13], yet mechanistic and epidemiologic evidence has not been fully explored.

The hypothesis presented herein is that salicylate therapy for influenza during the 1918–1919 pandemic resulted in toxicity and pulmonary edema, which contributed to the incidence and severity of early ARDS-like lungs, subsequent bacterial infection, and overall mortality. Pharmacokinetic data, which were unavailable in 1918, indicate that the aspirin regimens recommended for the "Spanish influenza" predispose to severe pulmonary toxicity.

A confluence of events created a "perfect storm" for widespread salicylate toxicity. The loss of Bayer's patent on aspirin in February 1917 allowed many manufacturers into the lucrative aspirin market. Official recommendations for aspirin therapy at toxic doses were preceded by ignorance of the unusual nonlinear kinetics of salicylate (unknown until the 1960s), which predispose to accumulation and toxicity; tins and bottles that contained no warnings and few instructions; and fear of "Spanish" influenza, an illness that had been spreading like wildfire.

More recently, influenza deaths have been attributed to salicylate. From the 1950s to the 1980s, thousands of deaths among children following influenza and other infections (eg, Reye syndrome) were unexplained until studies identified aspirin as the major contributor [14–16], and aspirin label warnings were followed by a disappearance of the condition [17]. Reye syndrome toxicity (vomiting, hyperventilation, delirium, and coma, with brain swelling and fat in the liver and proximal renal tubules) develops after ~4 days of salicylate therapy [14] with reported mean daily doses of 25 mg/kg [18]. (Adults with salicylate toxicity present mainly with abnormal consciousness and respiratory distress [19].) Also, a recent avian influenza A–associated fatality involved Reye syndrome and aspirin use [20], and several autopsies of persons who had avian influenza revealed hemorrhagic lungs, fatty liver changes, and swollen kidneys [21] consistent with salicylate intoxication.

Four lines of evidence support the role of salicylate intoxication in 1918 influenza mortality: pharmacokinetics, mechanism of action, pathology, and the spate of official recommendations for toxic regimens of aspirin immediately before the October 1918 death spike. (Grains of aspirin used in older texts are converted to milligrams as follows: 1 grain equals 65 mg).

ASPIRIN REGIMENS (DOSE AND SCHEDULE) RECOMMENDED IN 1918 ARE NOW KNOWN TO REGULARLY PRODUCE TOXICITY

In 1977, a US Food and Drug Administration panel [22] recommended that the maximum safe daily dose of aspirin for the general population was 4000 mg, with a mean hourly rate of 167 mg/h, and that "dosing regimens exceeding either this total daily dosage or mean hourly rate provide a significantly greater risk without a compensating therapeutic benefit" (p 35360). As an example of the unusual nonlinear kinetics of salicylate, the panel noted that simulations show that, after increasing the dose from 2 to 4 g daily (given every 6 h), "the total amount of drug in the body at steady state will increase from 1.3 grams to 5.3 grams, a 400% increase." In 2007, an evidence-based consensus guideline [23] recommended that anyone with an acute ingestion of 150 mg/kg or 6.5 g of aspirin equivalent, whichever is lower, warrants referral to an emergency department and recognized that, after multiple doses, it is difficult to generalize any dose associated with toxicity, because lower daily doses (2–3 g for several days) may lead to toxicity in some patients.

In the early 1900s, physicians treating serious conditions (eg, rheumatic fever) generally "pushed" salicylate until the appearance of toxicity and then backed off [24]. In 1918, dosing recommendations for pandemic influenza were similar to

these high-dose, hospital-based regimens, except that the recommendations for influenza generally offered no instruction for dose adjustment if toxicity occurred.

French's historic 1920 report for the British Ministry of Health [25] on the pandemic states that the aspirin dose was "15 to 20 grains" (975–1300 mg). No frequency was given. One London doctor "drenched" his patient with salicin: 20 grains (1300 mg) hourly for 12 hours nonstop [26]. Others suggested sodium salicylate, 6 grains (390 mg) over 3 hours for several days [27]. Aspirin was recommended for pulmonary edema [28]. On 26 September 1918, the US Navy recommended a cathartic and 5 grains (325 mg) of aspirin, warning against large doses [29]. However, the Navy's *Materia Medica* stated that the maximum dose was 1300 mg [30]. On 5 October 1918, *The Journal of the American Medical Association* [31] recommended aspirin: "The acetylsalicylic acid may be given in a dosage of 1 gm. (15 grains) every three hours…or a smaller dose combined with 0.1 gm. (2 grains) acetophenetidin, until symptomatic relief is secured" (p 1137). These recommended doses (1000–1300 mg), with frequencies ranging from hourly to every 3 hours, resulting in daily doses of 8–31.2 grams, are above the maximum safe dose defined above and would lead to accumulation, as noted below.

Hints of unusual pharmacokinetics and individual variation were noted before the pandemic but largely ignored. In 1906, Langmeade [32] observed "great variation in the amount required" (p 1824) for toxicity and reported a hospitalized child (receiving 325 mg every 6 hours) who, on day 4, developed vomiting, fever, dyspnea, cyanosis, and coma and died. He recommended caution early in treatment so "the personal factor may be estimated." In 1913, Hanzlik [24] studied records of 400 hospitalized persons treated with a common regimen, 10–20 grains of a salicylate hourly with sodium bicarbonate until toxicity occurred (headache, nausea, tinnitus or deafness, delirium, or hallucinations). He found that the mean toxic dose of aspirin for male persons was 165 grains (10,725 mg), a probable overestimation, because sodium bicarbonate greatly enhances salicylate excretion. The toxic dose of synthetic salicylate in males ranged from 1300 to 31,200 mg.

The development of tests to measure salicylate in the blood in the 1940s allowed Alvin F. Coburn [33] of the US Navy, while studying rheumatic fever, to find that a dose of 10 g daily led to levels that averaged 36 mg/dL on day 3 in 9 adults. In 1948, Graham and Parker [34] were among the first to correlate the blood salicylate level with symptoms of toxicity. First, after studying 58 individuals, they found considerable variation in the level at which symptoms developed, such as vomiting (16.3–38.6 mg/dL), hyperventilation (21–44.2 mg/dL), pulmonary edema (49.4 mg/dL), and severe dyspnea (46–53.6 mg/dL). They also studied 33 patients who attained levels of 35 mg/dL during the first 7 days of therapy and found the following severe toxicities: hyperventilation (in 33%), vomiting (in 30%), marked sweating (in 12%), headache (in 12%) severe drowsiness (in 12%), confusion (in 6%), severe dyspnea (in 6%), excitement (in 6%), epistaxis (in 6%), vertigo (in 3%), pulmonary edema (in 3%), and hemorrhage (in 3%). The incidence of these toxicities may be higher, because administration was halted when hyperventilation occurred. A retrospective study [35] of 56 salicylate-intoxicated adults, with intoxication defined as a peak salicylate level $\geqslant$30 mg/dL, found 6 patients (11%) with noncardiogenic pulmonary edema. For adults aged >30 years, the incidence of noncardiogenic pulmonary edema was 35%. Interestingly, none of 55 consecutive intoxicated pediatric patients had pulmonary edema.

In the 1960s, scientists learned why toxicity occurs with intense aspirin therapy: salicylates have unusual and complex pharmacokinetic characteristics that predispose to accumulation, rendering both dose and schedule critically important. In 1965, Levy [36] showed that, when the amount of drug in the body reaches ~360 mg, the half-life increases as elimination changes from first order to zero order. Later, Bardare et al [37], who studied children, observed half-lives of ~5 h at a dosage of ~50 mg/kg per day (3500 mg in a 70-kg person), of ~15 h at dosages of 75–95 mg/kg per day, and of ~40 h at dosages >100 mg/kg per day. Dosing at intervals of the half-life or less will lead to accumulation.

In addition to the saturable metabolism described by Levy and colleagues [36, 38, 39], accumulation of salicylate can occur for other reasons, including individual variation in elimination rate [38], reduced renal excretion [40], and low urine pH [41]. Higher doses, as mentioned above, slow elimination [42] and enhance the volume of distribution [43]. Acidosis [44] and hypoproteinemia [45] increase brain uptake and toxicity. The salicylate level [42] and the level at which toxicity occurs [24, 34] vary among individuals. Therefore, it is likely that severe salicylate intoxication, including pulmonary edema, developed in some persons who followed the recommended 1918 dosing regimens.

SALICYLATES CAUSE IMMEDIATE LUNG TOXICITY AND MAY PREDISPOSE TO BACTERIAL INFECTION BY INCREASING LUNG FLUID AND PROTEIN LEVELS AND IMPAIRING MUCOCILIARY CLEARANCE

The occurrence of pulmonary edema in humans with salicylate intoxication is well documented [19, 35]. Increased pulmonary vascular bed permeability to fluid and protein, decreases in arterial pO2, and increases in postmortem extravascular lung water followed salicylate administration in sheep [46]. Salicylate also depresses the lung's mucociliary transport system [47].

THE PATHOLOGY OF THE EARLY DEATHS IS CONSISTENT WITH ASPIRIN TOXICITY AND VIRUS-INDUCED PATHOLOGY

Autopsy reports by pathologists of the day describe extremely wet, sometimes hemorrhagic lungs in early deaths. On 23 September 1918 at Camp Devens in Massachusetts, 12,604 soldiers had influenza, and 727 had pneumonia; after examining the lungs of a dead soldier, Colonel Welch concluded, "This must be some new kind of infection or plague" [48, p 190]. What struck E. R. Le Count [49], consulting pathologist to the US Public Health Service, as most unusual was the amount of lung tissue actually "pneumonic" seemed "too little in many cases to explain death by pneumonia." He saw a thin, watery, bloody liquid in the lung tissue, "like the lungs of the drowned," as well as pleural exudates with small hemorrhages unlike those seen in "any other form of acute pneumonia of which I am familiar." Importantly, he also noted the brain was "quite regularly swollen," the kidneys were "regularly the seat of cloudy swelling," and the liver had "superficial fatty change," (changes noted in children with salicylate intoxication; see below). He concluded, "It is difficult to believe that a disease with so many distinctive features and…novelty…can fail to possess a correspondingly definite etiology." Brain weight was increased by 100–200 g in ~50% of persons, most likely indicating cerebral edema; cerebral bleeding was common [9, 10]. Wolbach [50], chief pathologist at the Peter Bent Brigham Hospital in Boston, Massachusetts, found bacterial infection in late deaths, yet a person dying on day 2 exhibited edema and congestion of the lung, a purpuric rash, and no bacterial growth. He surmised a natural progression from the early lesion to the bacterial lesions: "Two types of lungs stand out." In early deaths, the lungs were "dark red and wet…dripping wet." French [25] described the lesion as "albuminuous, non-cellular, coagulable.…One realized that this albuminous exudate…was the probable cause of the cyanosis." The exudates were "so entirely unlike what is met with in any ordinary forms of pneumonia that they seemed to be essential importance, the other changes—haemorrhages, broncho-pneumonia and so on—being super additions.…"

Although these pathology findings have been induced with the 1918 influenza virus in models [6], they are also consistent with aspirin toxicity. A study of 177 adults with aspirin toxicity (and a 15% mortality rate) found the most common presentations were depressed consciousness (61%) and respiratory failure (47%), even "at therapeutic levels" [19]. Autopsy findings for patients with the 26 fatal cases were pulmonary edema (46%), ulcers (46%), cerebral hemorrhage (23%), and cerebral edema (31%). Coagulation disturbance or thrombocytopenia was found in 38%. A detailed autopsy of an adult with aspirin poisoning revealed cyanosis, pulmonary congestion, alveolar hemorrhage, subpleural and subepicardial hemorrhages, petechiae, cloudy swelling of the kidneys, and fatty degeneration of the liver [51, 52]. ARDS-like disease has also been reported [53]. Children with aspirin toxicity (or Reye syndrome) are less likely than adults to present with pulmonary edema [35], although in addition to brain swelling, fatty liver, and cloudy swelling of the kidneys [54, 55], some have pulmonary edema [55, 56], "frothy, blood-tinged fluid" [57], and lung hemorrhages [54].

A report from Camp Dix noted, "The disease was a veritable plague. The extraordinary toxicity, the marked prostration, the extreme cyanosis and the rapidity of development stamp this disease as a distinct clinical entity heretofore not fully described.…Pneumonia is an important but somewhat secondary factor" [58, p 1817]. Salicylate toxicity is often overlooked [59] because another condition is present, the dose is thought to be trivial, and the symptoms (hyperventilation, vomiting, sweating, headache, drowsiness, confusion, dyspnea, excitement [salicylate jag], epistaxis, vertigo, pulmonary edema, and hemorrhage) are nonspecific [34]. In 1918, differentiating progressive salicylate intoxication from infection pathologically or clinically, "the dyspnea lasts from a few hours to a day…followed by respiratory failure, circulatory collapse, convulsions, and death" [40], was almost impossible.

ASPIRIN ADVERTISEMENTS IN AUGUST 1918 AND A SERIES OF OFFICIAL RECOMMENDATIONS FOR ASPIRIN IN SEPTEMBER AND EARLY OCTOBER PRECEDED THE DEATH SPIKE OF OCTOBER 1918

In May 1918, usual but highly contagious influenza was publicized in Spain (hence, "Spanish influenza") [48]. In June, after 6 weeks of usual influenza in Europe, serious pulmonary lesions and deaths increased in those "admitted to the special influenza centres," especially those with an "old-standing renal lesion" [60]. In July, increased mortality of young Londoners was documented [61].

Farbenfabriken Bayer's worldwide efforts had left few places lacking aspirin. In the United States, Bayer's giant factory produced aspirin under "American" management. After Bayer executives were charged with violating the Trading with the Enemies Act in August 1918, advertisements encouraged confidence in aspirin [62]. The "Spanish lady" came to the United States and struck 2000 Navy men in Boston in late August. The majority recovered, but oddly, 5%–10% developed a "very severe and massive bronchopneumonia," which, in many, lacked an accompanying leukocytosis [63]. Influenza spread.

Official recommendations for aspirin were issued on 13 September 1918 by the US Surgeon General [64], who stated aspirin had been used in foreign countries "apparently with much success in the relief of symptoms" (p 13), on 26 September 1918 by the US Navy [29], and on 5 October 1918 by *The*

Journal of the American Medical Association [31]. Recommendations often suggested dose regimens that predispose to toxicity as noted above. At the US Army camp with the highest mortality rate, doctors followed Osler's treatment recommendations, which included aspirin [48], ordering 100,000 tablets [65]. Aspirin sales more than doubled between 1918 and 1920 [66].

The number of deaths in the United States increased steeply, peaking first in the Navy in late September, then in the Army in early October, and finally in the general population in late October [67]. Homeopaths, who thought aspirin was a poison, claimed few deaths [11, 48]. Others may have suspected that aspirin was responsible. On 23 November, 1918, Horder [68] wrote in *The Lancet* that, for "intensely toxic cases…aspirin and all so-called febrifuge drugs must be rigidly excluded from the treatment" (p 695)

In summary, just before the 1918 death spike, aspirin was recommended in regimens now known to be potentially toxic and to cause pulmonary edema and may therefore have contributed to overall pandemic mortality and several of its mysteries. Young adult mortality may be explained by willingness to use the new, recommended therapy and the presence of youth in regimented treatment settings (military). The lower mortality of children may be a result of less aspirin use. The major pediatric text [69] of 1918 recommended hydrotherapy for fever, not salicylate; its 1920 edition [70] condemned the practice of giving "coal tar products" in full doses for reduction of fever. The occurrence of Reye syndrome–like illness before the 1950s is debated and consistent with the fact that children's aspirin was not marketed until the late 1940s. Varying aspirin use may also contribute to the differences in mortality between cities and between military camps.

To determine the proportion of virus-induced pathology, subsequent bacterial infection, and overall 1918 pandemic mortality attributable to salicylate, experimental models and analysis of primary consecutive individual treatment and pathology records are needed. Prospectively, aspirin should be investigated in countries where aspirin is used for influenza.

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