

ROLE FOR HYPOCHLORITE SAPONIFICATION IN SEMMELWEIS'S SUPPRESSION OF PUERPERAL FEVER EPIDEMICS

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Abstract

The most prominent product of the Vienna General Hospital was Ignaz Semmelweis, who was the first to use a chemical antiseptic to counteract the large scale outbreaks of puerperal fever which had periodically decimated maternity wards ever since those institutions were established. Semmelweis introduced the compulsory use of bleach and nail brushes to wash gynecologists' hands, before patient examinations, to remove pathological material and lubricating oil. He worked with little chemical knowledge and no possible knowledge of microbial pathology in the significant years prior to 1847. He was, strangely by twenty-first-century standards, influenced by ideas of miasmas in his efforts to suppress pathology by suppressing the clinging odor of pathology with chlorine. His chemical breakthrough has saved many thousands of babies' and mothers' lives. It has been assumed that the chemical mechanism for Semmelweis's antiseptic procedure was oxidation. The present work suggests that the striking suppression of puerperal fever was achieved by saponification in addition to oxidation.

Introduction

Ignaz Philipp Semmelweis (1818-1865) (1) was a gynecologist who worked in the *Allgemeines Krankenhaus der Stadt Wien* (Vienna General Hospital) which was and is a prestigious teaching institution. Despite highly qualified and influential medical staff, the hospital, like many lying-in hospitals for pregnant women, was pe-

riodically overwhelmed by outbreaks of puerperal fever which were fatal for large proportions of the mothers and babies occupying the hospital (2). Medical practitioners, including Semmelweis early in his career, had little idea of the cause of puerperal fever, often resorting to concepts we find strange today, such as theories of pathological miasmas (3, 4).

...when the linen and the bedding does not always present the necessary degree of cleanliness; then the air in the wards can become impregnated with decomposed matter, either because the exhalations of the puerperae are not removed by ventilation, or because decomposed matter is carried into the lying-in wards from the general hospital, from the nearby deadhouse, [or] from the open sewers outside the lying-in hospital ... A locale can only cause childbed fever [puerperal fever] when it is so polluted with decomposed matter that the exhalations of decomposed matter mixed with the atmospheric air penetrates into the genital organs of the patients...

Odors from lesions, death and decay must have been appalling in hospitals of the time, and the high standards of cleanliness practiced now were not seen in the mid nineteenth century. This is shown spectacularly by the observations of Young (5) and Berkeley (6) of repeated *Coprinus* basidiocarp crops growing from a patient's bed. *Coprinus* is a common dung fungus which we assume developed on patient dung seeping through the bed, not cleaned up for as long as the fungus needs for development of fruiting bodies (approximately one week on dung

in the experience of one of us, MW), then developing a second crop from the imperfectly cleaned bed.

By 1847, however, Semmelweis was able to conclude from his observations of the persistent odor of medical practitioners' hands, especially after autopsies, and analysis of his own statistics, that puerperal fever was a nosocomial disease (i.e., acquired in hospitals) which was initiated by transfer of infectious odiferous material of unknown nature from patient to patient by medical workers themselves, causing the intense and destructive but local outbreaks of disease. Localized to patients touched by the medical practitioners, the disease often developed as linear trails of infected patients which traced the path of the doctor moving from patient to patient in the ward some days previously.

Semmelweis's work on disinfection, which was discussed in 1840s Vienna (2) and finally published in 1861, predates publication of Lister's work (7) by two decades and the discovery of *Streptococcus pyogenes* in pathological discharges from puerperal fever patients by Pasteur (8) by more than three decades. This is why it took some time for Semmelweis to discover that pathological material absorbed to skin and the oil used for finger lubrication (9) was a serious danger to patients. Despite Semmelweis's discovery and his suppression of puerperal fever at Vienna he argued with influential proponents of miasma theories and was acrimoniously dismissed (2, 3). It was only after returning to his native Hungary and a long drawn-out process of persuasion and repeated delay that in 1861 the statistics and chemical methods of Semmelweis were widely accepted, especially regarding the suppression of periodic outbreaks of puerperal fever by handwashing and nail scrubbing with calcium hypochlorite, these being summarized in the following circular to district authorities from the Presidential Council of Hungary. His method varied over time, but the following circular is a good summary of the final procedure of Semmelweis (10).

To All Whom It May Concern,

Dr. Ignác Fülöp Semmelweis, Royal Hungarian University Professor, in his excellent book on puerperal fever believes that it is caused by decomposed, organic animal material introduced into the body of parturient women.

Dr. Semmelweis's opinion is embraced by the medical faculty of the Royal Hungarian University and is shared by the best scientists and physicians.

There can be no other reasonable prophylactic method than to prevent the introduction of any infectious, decomposed material into the body of the

lying-in patient. For this reason, the author proposes that physicians and midwives, before touching any infectious agent, should oil their hands profusely, in order to prevent the material from penetrating into the pores of the skin. Subsequently, by washing their hands well with soap and chlorine (*chlorniturn calcis* [sic (11)]) to neutralize any remaining infectious substance, they should go on doing this until they find their hands smooth and **slippery** [emphasis added].

By this method the hands can be made perfectly clean. It should however be remembered that infection can be introduced not only by means of the examining fingers, but also through any objects infected by contact with decomposed animal material. Consequently, these must also be disinfected before being brought into contact with the genital organs, or else should be discarded: such objects can be surgical instruments, bed-clothes, sponges, etc.

As the infectious substances can be carried over by air too, it is imperative that the wards should be well and frequently aired and that exhalations and exudations should be removed before decomposition.

These preventive measures which have been examined and found indispensable should be introduced and observed in hospitals, obstetric and lying-in wards and in private practice. Therefore, we call upon all officials to advise physicians, surgeons, obstetricians and midwives to study the prophylactic measures proposed by Prof. Semmelweis in his book on puerperal fever and to introduce them in hospitals and elsewhere.

September 1st, 1862

Semmelweis recognized a requirement to break down, destroy or remove pathological matter, even before *Streptococcus pyogenes* was recognized as the principal cause of puerperal fever (8). Modern scientists, who are familiar with the work of Pasteur and Koch (12) and Duchesne (13), associate infectious pathology with cellular parasites including airborne suspensions of bacteria. This is something that adds confusion to readers of Semmelweis because he was a miasma theorist and when he wrote of airborne particles he meant chemical particles while later readers may mistakenly assume the particles he referred to were bacteria not molecules. The influence of miasma theory on Semmelweis was fortunate for his patients, because it led to his use of molecules that suppress chemical odors very well by chemical reaction (sometimes using dissolved dichlorine gas and sometimes calcium hypochlorite). Semmelweis used the benchmark of odor to judge if pathological cadaverous matter had been destroyed. He destroyed the odor intentionally but also unintentionally destroyed bacteria. This is a great example of correlation without causation which had a co-

incidental good effect of correctly directing future action.

Nobody can suggest a precise mechanism which accounts for his chemical disinfection except general destruction of organic matter and damage to a complex mechanism (pathogens), where the form of damage is too difficult to describe. It has been assumed that Semmelweis achieved effective hand sanitization in two broad ways. One was by oxidation reactions (summarized in 14) which killed bacteria, especially *Streptococcus pyogenes*. This was supplemented by scrubbing, which dislodged pathological matter and created a larger surface area for oxidation, especially for matter trapped under fingernails. Semmelweis's sanitization method has an additional sign that is often ignored, which is to keep washing until hands felt slippery. This suggests that an additional, third part of his sanitation method is important, i.e., saponification of the physician's own natural oils and lubricant oil to make soapy material felt by gynecologists as slippery when they washed their hands with hypochlorite. Saponification is important here because it turns oils to soaps and while soaps do not have strong antiseptic properties they instead emulsify fats and oils. This dislodges bacteria and causes degerming of skin (15). We suggest that the use of oil (presumably triglycerides), followed by soap and hypochlorite caused this additional component of sanitation. Handwashing was enhanced by saponification of oil which increased soap in the wash mixture and undermined attached pathogens. This is useful because pathogens adhering to skin or under oil may be easily washed away down the drain in this process.

To achieve chemical disinfection Semmelweis used *chlorina liquida* (6% w/v chlorine gas in water (16)) in his earlier work or chlorinated lime (17) in his later work. A conspicuous and unique feature of modern domestic bleach is that it makes hands feel very slippery immediately and in a way that is unique. It is perceived differently to the slipperiness of lubricating oil or of ordinary soap. This is presumably due to autosaponification. Modern household bleach has a high pH (around 12, (18)), which might cause saponification, but we suspected that this does not account for all the phenomena seen by Semmelweis, especially as *chlorina liquida* was an effective disinfectant.

The use of oil in gynecology gave us a technical advantage in solving this question, namely that lubricating oil is much more uniform than human skin lipids so analysis using infrared (IR) spectroscopy was a possibility for testing our ideas. We used commercial soybean oil, which we assume is similar to that used for lubrication in nineteenth-century gynecology (9), to react with domes-

tic bleach to determine if saponification of triglycerides by hypochlorite can take place under conditions similar to Semmelweis's procedure for hand washing.

Methods

We have examined the method of hypochlorite disinfection ourselves. While many researchers have reacted chlorine and hydrocarbons using rigorous chemical methods including high temperatures or with a catalyst (19) we assumed these experiments were not relevant to hospital disinfection. It is important that all these methods were conducted at room temperature. The bleach solution used contained 6.9% sodium hypochlorite and had 5.7% available chlorine (Walmart, Bentonville, Arkansas). Commercial food grade soybean oil was used (Publix, Lakeland, Florida). Oil (20 mL, 15.044 g) and bleach (20 mL) were added to a 50 mL Falcon tube and shaken to an emulsion by hand. The mixture was incubated at 25 °C for 2 weeks and white solid saponified material accumulated at the interface. This time was used to observe that no more saponified material appeared and we assumed that reaction had run to completion. The mixture was then centrifuged at 5000 g for 10 minutes. The interface material was a firm white slippery solid. The upper oil layer, white interface material and lower aqueous layer were removed and stored separately. Water adhering to the interface material was viscous. This viscous material had air introduced into it using a 1-mL pipette tip and lingering bubbles were produced. A small amount was transferred to a 1.5-mL Eppendorf tube and shaken by hand. Foam was produced. The white solid was washed with 2 × 2 mL water then air dried for 14 days yielding 13.4 mg of material. There was presumably additional saponified material which was soluble in the aqueous and oily phases but not harvested.

Infrared spectra (Figure 1) were recorded using a Perkin Elmer Spectrum One FT-IR equipped with ATR. NMR spectra were recorded using the soluble portion of the acidified white solid material in CDCl₃. Briefly, white solid (10 mg) was suspended in 0.7 mL of D₂O and 20 μL of 20% DCl in D₂O was added to the mixture. CDCl₃ (0.6 mL) was added to the mixture. This was allowed to separate at room temperature for 15 minutes, giving an upper aqueous layer, and lower CDCl₃ layer with undissolved white solid suspended between these two layers. The bottom layer (CDCl₃) was pipetted out and filtered through an anhydrous Na₂SO₄/glass wool short column directly to an NMR tube. The ¹H NMR spectra were obtained using a Bruker Avance 400 MHz device (Figure 2).

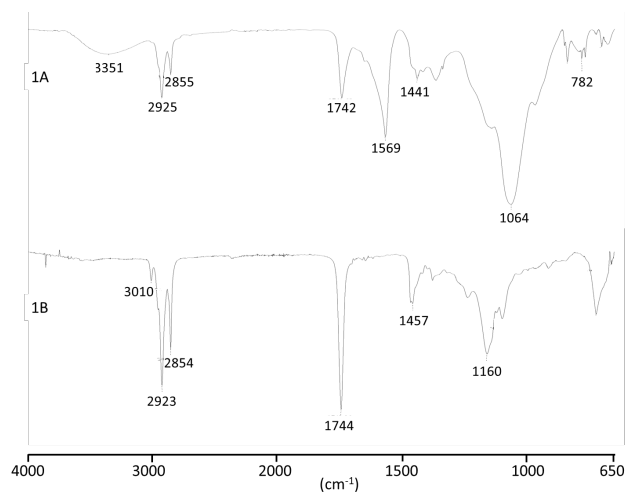


Figure 1. A) IR spectrum of the white solid precipitated in water layer. B) IR spectrum of soybean oil.

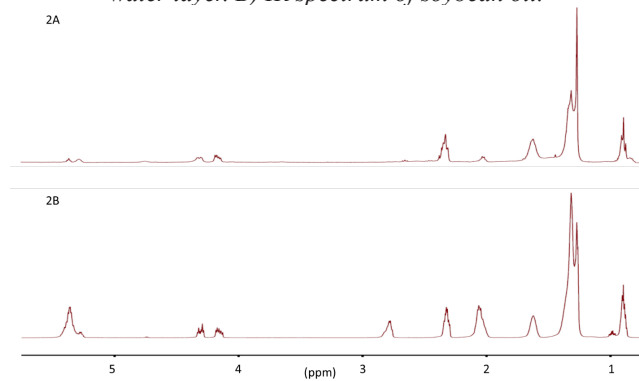
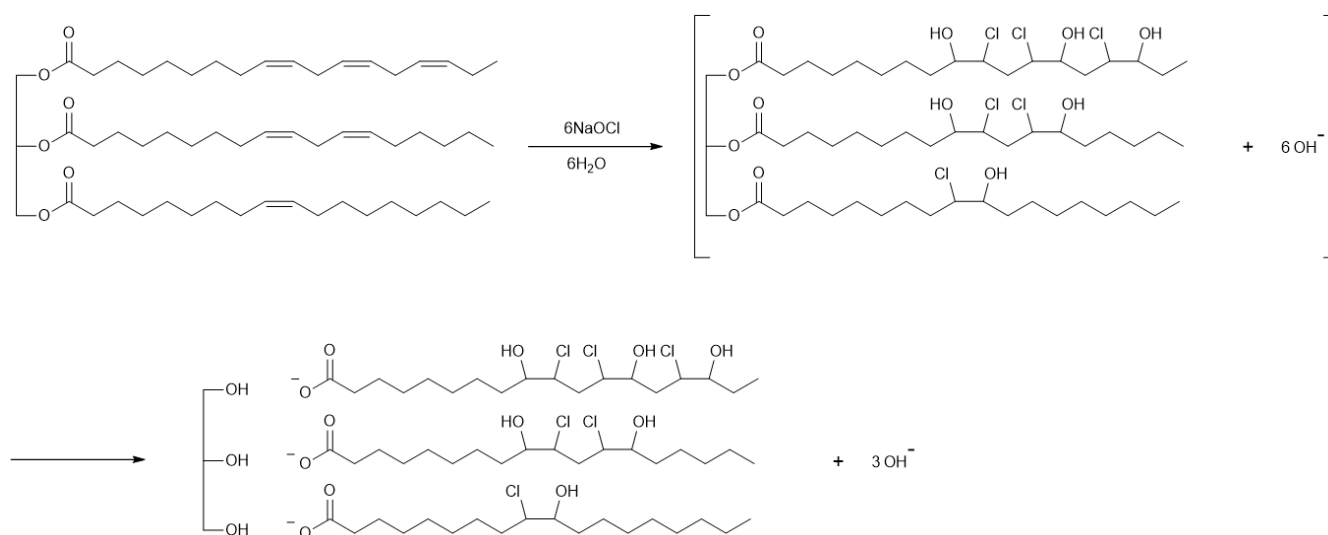


Figure 2. A) NMR spectrum of the protonated white solid. B) NMR spectrum of soybean oil.

Results and Discussion

It was surprisingly easy to produce a solid soap using oil and hypochlorite (Scheme 1), and this material was recovered easily by pulling the solid out of the reaction vessel (50-mL Falcon tube) and blotting to remove excess liquid aqueous and oily material. The IR spectrum of this white solid soap supports the idea that triglycerides underwent saponification to form the carboxylate of fatty acids as seen in figure 1A which shows the IR spectrum of the white solid material. A broad band at 3100–3700 cm⁻¹ is attributed to the O–H stretching of alcohol. The bands at 1569 and 1441 cm⁻¹ are attributed to asymmetric and symmetric COO⁻ stretching. The band at 782 cm⁻¹ is attributed to C–Cl stretching. A comparison between IR spectrum of the white solid (Figure 1A) and that of soybean oil (Figure 1B) shows disappearance of C–H stretching of sp² carbons at 3010 cm⁻¹. The spectrum also reveals that unsaturated bonds were oxidized by hypochlorite to yield chloro- and hydroxy- groups.

Figure 2A shows ¹H NMR spectrum of the mixture in CDCl₃ layer. A comparison between ¹H NMR spectrum of the protonated white solid soap (Figure 2A) and that of soybean oil (Figure 2B) shows disappearance of CH (5.37 ppm) of sp² carbons at the unsaturation points and CH₂ (2.78 and 2.06 ppm) next to the sp² carbons. This supports the conclusion that these double bonds have been replaced with hydroxyl groups or chlorine atoms.



Scheme 1. The reaction shows a triglyceride containing oleic acid (C18:1), linoleic acid (C18:2) and linolenic acid (C18:3) as a representation of soybean oil. First step, unsaturated bonds of the triglyceride are oxidized by sodium hypochlorite and water from bleach solution to yield chlorides and hydroxyl groups along with hydroxide ions. Second-step, base promoted saponification occurs to yield glycerol and carboxylates of fatty acids.

From all of this we suggest an additional component to Semmelweis's method of sanitation where the mechanism of oxidation was previously assumed to account for his success. This additional component is that saponification is important to the process especially because in the nineteenth century gynecologists' fingers were lubricated with oil. Saponification is important because it breaks the oil into soluble products and undermines attachment of pathological bacteria. These saponification reactions are relevant because hypochlorite and oil can readily form soap seen in the form of white solid material and felt as slippery.

This disinfection method was overtaken later by other methods and materials, such as washing with carbolic soap (20, 21), partly because Semmelweis was very slow to publish his work. Also, hypochlorite hand-washing is an uncomfortable process (22), causing skin irritation, eyewatering and nausea in the experience of one of us (MW). This made the process unpopular with some of Semmelweis's colleagues who resisted his efforts effectively (2).

To some flattering later historians (2) Semmelweis's work is viewed as a step in the inevitable path to the modern age and a great example of early and saintly scientific success. Semmelweis was successful in suppression of puerperal fever while he worked in Vienna and also in hospitals he worked in later. However, his work was disconnected from later achievements in microbiology, such as those of Pasteur, Koch and Lister, and largely ignored from the late 1840s to the early 1960s. This was because several factors operated against him. He was very slow to publish: work done in 1847 was only published in book form in 1861. There were some brief descriptions of his Vienna work by colleagues but fourteen years is a long time to wait for details! He was also marginalized by clashes with colleagues and senior members of his profession, on subjects medical, political and emotional (23). Those clashes escalated to the point of him abruptly leaving Vienna (1850), the place where his work was discussed and written of, to a small degree, in German. He returned to Pest in his native Hungary, where his work was then discussed in Hungarian, which is a much less accessible language to most scientists. Since 1850 Semmelweis was admired in Hungary but neglected elsewhere. However, in 1966 Semmelweis's work was revived as an influential example (24) and he has since been portrayed as a scientist of great achievement (2). Nevertheless, detailed reading shows some complexity and feet of clay. He was dogmatic, but changed his dogma three times (25), to the exasperation

of his contemporaries. This dogmatism included verbal anger and ultimately writing, in the form of insulting open letters to his fellow gynecologists (3). Recently he has taken on the additional reputation of a martyred saint because as his behavior became more and more alarming to his relatives and friends he was tricked into captivity in a mental hospital where the warders, following the standards of the time, beat him severely. Semmelweis contracted sepsis from one of the wounds and ironically died of septic disease similar to puerperal fever (26).

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About the Authors

Michael Witty is still an empirical scientist, publishing from 1989 in ecology, botany, zoology, human pathology, biotechnology, microbiology, microscopy, molecular biology, biochemistry, organic chemistry, inorganic chemistry, crystallography, scientific education, intellectual property, history, English and ancient literature. He has lived or worked on every continent except Antarctica, which would be absurd.

Theppawut Ayudhya practices syntheses focusing on polymer materials, inorganic synthesis, and his research involves a wide range of applications from medicine, chemical sensors, to energy storage materials.

2022 Sarton Medalist

Margaret W. Rossiter has been named the 2022 Sarton Medalist by the History of Science Society (HSS). Rossiter is best known for her work on women in science and the structural inequalities under which they have worked or been excluded. Those inequalities were documented in her three-volume *Women Scientists in America* as well as in influential articles such as "The Matthew Matilda Effect in Science." Her work has been used by policy groups such as the US National Science Foundation to understand barriers to participation and promote inclusion of women in science, and Rossiter herself has worked on issues of inclusion with the American Association for the Advancement of Science (AAAS), the Fulbright Foundation and the National Institutes of Health.

Rossiter earned an A. M. from Radcliffe College, an M. S. from the University of Wisconsin-Madison, and an M. Phil. and Ph.D. from Yale University. She is Marie Underhill Noll Professor of History of Science Emerita at Cornell University. She served HSS as a co-founder of its Women's Caucus and as editor of both *Isis* and *Osiris*. She has been previously named a Guggenheim Fellow, a MacArthur Fellow and a Fellow of the AAAS.

This item drew on information in Jessica Ratcliff's blog post at <https://hssonline.org/blogpost/1987463/475363/Margaret-W-Rossiter-2022-Sarton-Medalist>.