

# Therapeutic Properties of *Silver*:

## AN HISTORICAL AND TECHNICAL REVIEW

by S.M. Foran

*“The discovery and development of antibiotics for the treatment of bacterial infections must be regarded as one of the most significant medical achievements of the twentieth century. Unfortunately, as we enter the new millennium many of our existing antibacterial agents are under threat from the widespread emergence of bacterial resistance. Furthermore, the pace of emergence of antibiotic-resistant bacteria has outstripped the discovery of new antibiotics. New agents are therefore urgently needed to counter the threats posed by antibiotic-resistant organisms.”*

--Ian Chopra

Infectious disease has been, and continues to be, man’s mortal enemy. In the early part of the 20<sup>th</sup> Century, optimism soared as antibiotics were introduced into the medical arsenal. After the discovery of penicillin in 1928 and the subsequent development of a method for its large-scale production, “penicillin became known as the ‘wonder drug,’” and antibiotics “became the standard treatment for bacterial infections.”<sup>1, 2</sup> New and even more powerful infection fighters followed penicillin as “super antibiotics” were developed. Man’s final conquest over the deadly germ appeared within reach, and, in 1969, the Surgeon General of the United States announced to Congress that “the time [had] come to close the book on infectious disease.”<sup>3</sup>

The Surgeon General’s declaration of victory, however, proved to be an optimistically blind one. As

early as 1945, “shortly after penicillin’s debut into hospitals,” strains of *Staphylococcus aureus* were found to be “resistant to the drug.” Methicillin, a semi-synthetic penicillin, was introduced in 1960, but, after only a year of its being used, “a study reported strains resistant to it.” By 1991, over 40% of *Staphylococcus aureus* strains were methicillin-resistant.<sup>4</sup> (Methicillin-resistant *Staphylococcus aureus* is the strain of bacteria commonly referred to as MRSA.) (See Fig. 1) Because of the resistance that developed against penicillin and methicillin, vancomycin, a “last resort” antibiotic, became a popular alternative in many U.S. hospitals. However, some strains of bacteria

soon began to develop a resistance to this powerful drug as well.<sup>5</sup> Even now, with over one hundred antibiotics available, there is a fear “that many bacteria will become resistant to all antibiotics, plunging humanity back into the conditions that existed in the pre-antibiotic age.”<sup>6</sup>

The development of wide-scale antibiotic resistance has been linked directly to the overuse of antibiotics. (See Fig. 2) In 1994, the Office of Technology Assessment was commissioned by Congress to study the impacts of antibiotic-resistant bacteria. According to the OTA report, published in 1995, “as much as 50 percent of antibiotic use is inappropriate because the uses do not benefit the patient [and merely] increase the emergence and spread of antibiotic-resistant bacteria.”<sup>7</sup> The over-prescription of antibiotics is also compounded by the fact

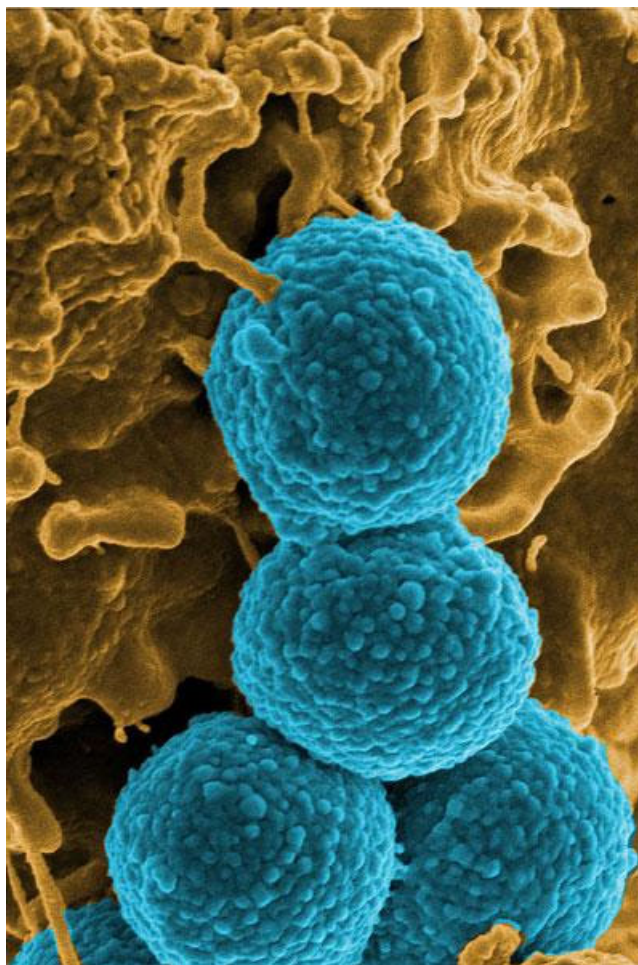


Fig. 1 The round, pea-like objects are methicillin-resistant *staphylococcus aureus* and the darker objects are a human white blood cell. Both objects have been magnified 30,000 times.

that many infections are actually viral in origin and are, therefore, non-responsive to antibiotic treatment.<sup>8, 9</sup>

Mass exposure has become an even greater concern as an array of antibiotics enters the food chain through livestock and dairy products. Nearly half of the antibiotics used in the United States are utilized “in the production of food animals,” and the most commonly used antibiotics in animal husbandry are “penicillin and the tetracyclines.” Although many government agencies, such as the FDA and the National Academy of Sciences, do not believe that this should cause undue concern, the OTA determined that “there is no question that agricultural uses of antibiotics select for antibiotic-resistant bacteria just as do medical uses.”<sup>10</sup> (*Selection* is the process by which an antibiotic kills off non-resistant bacteria, “leaving the antibiotic-resistant bacteria to multiply and flourish.”)<sup>11</sup>

It is an understatement to say that this is a serious problem. It is so serious, in fact, that an Interagency Task Force on Antimicrobial Resistance was created in 1999. The Task Force is co-chaired by the CDC, the FDA, and the NIH.<sup>12</sup> Yet, in spite of the public action plan that was developed by this task force, the problem continues to grow worse. According to a government study that was published in the *Journal of the American Medical Association* in 2007, infections caused by antibiotic-resistant bacteria are on the rise. Researchers estimated that over 94,000 patients “developed an invasive infection

from the [MRSA] pathogen in 2005 and that nearly one of every five, or 18,650 of them, died.”<sup>13</sup> As frightening as this statistic is, it should be noted that this study only reported deaths linked to a single antibiotic-resistant bacteria. The urgency of this issue is heightened by the fact that, despite continued research, there are currently no sources for developing new antibiotics. Medical science has literally exhausted the antibiotic field, and all recent additions are simply “derivatives or new applications or formulations of antibiotics already on the market.”<sup>14</sup>

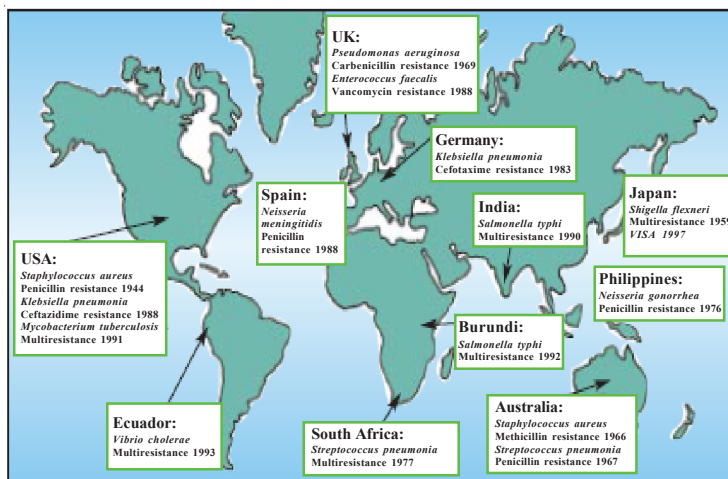


Fig. 2 The global emergence of antibiotic-resistant pathogenic bacteria. Examples are shown of the first major reports of clinical isolates expressing resistance to individual antibiotics, or groups of antibiotics.

### An Overlooked Solution to a Modern Problem

As we continue to grapple with the undeniable seriousness of this issue, some researchers are looking for a solution in what, to many, may seem an unlikely place. The long sought answer to this problem may be found in the form of an ancient and powerful remedy known for its antimicrobial properties: silver. (See Fig. 3)



Fig. 3 Crystals of silver metal.

We can trace the medicinal use of silver back to the end of the 8<sup>th</sup> Century when Avicenna employed “silver filings as a blood purifier,” as well as to treat offensive breath and palpitations of the heart.<sup>16</sup> The Greeks of antiquity “drank wine from silver cups because they thought that it would minimize the outbreak of disease.”<sup>17</sup> And during the Medieval Era, when the plague was a common threat, wealthy families used silver plates and utensils because of the belief that silver had “disease-fighting properties.”<sup>18, 19</sup> Silver nitrate



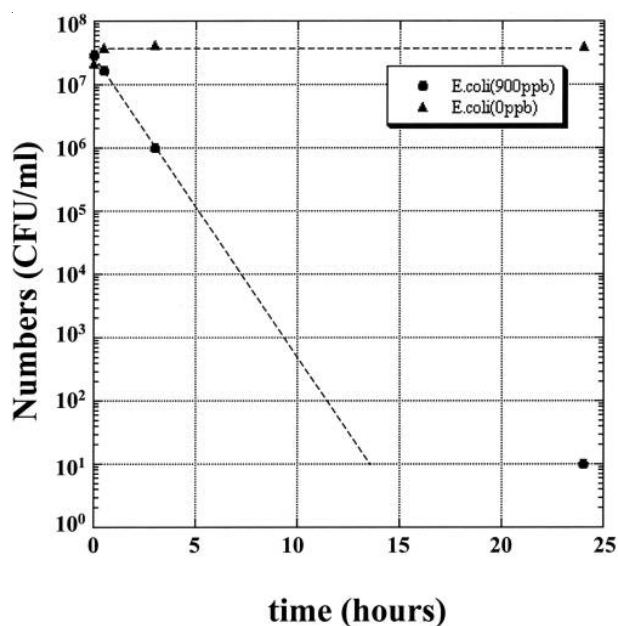


Fig. 4 Viability of *E. coli* cells versus time, as a result of reactions with 900-ppb and 0-ppb silver ion solutions. Viable cells were enumerated on an agar plate containing 1 g/liter glucose, 2.5 g/liter yeast extract, and 5 g/liter tryptone by the colony count method, after incubation at 35°C for 24 h.

was also used at this time for “the treatment of nervous system disorders such as epilepsy and tabes dorsalis [a degeneration of the spinal cord due to syphilis].”<sup>20</sup> In the 19<sup>th</sup> and early 20<sup>th</sup> Centuries, “the medical industry made use of silver’s germicidal properties.”<sup>21</sup> In fact, “colloidal silver was accepted by the [FDA] as being effective for wound management in the 1920’s.”<sup>22</sup> It was not until the introduction of penicillin that “interest in silver as an anti-microbial medicine declined,” and this may have been due, in part, to the fact that pharmaceutical companies could not take out any patents on silver.<sup>23</sup>

By the 1960’s, silver was again used for the “management of burn patients,” but it was not until more recent years that silver began to make more of a comeback.<sup>24</sup> It is now being used in water filtration: both the CDC and the WHO recommend using silver filters as a way to purify water in developing countries, and Soviet scientists have used silver to sterilize recycled water aboard the MIR space station.<sup>25, 26</sup> The U.S. Forest Service has even explored the possibility of using silver as a wood preservative.<sup>27</sup> The medical industry has also begun employing silver again: “silver dressings are used regularly in hospital settings to help control infections in major wounds and

burns,” silver-coated endotracheal tubes are used to prevent bacterial colonization and avert ventilator-associated pneumonia, and central venous catheters are impregnated with silver in order to reduce the rates of catheter-related infections.<sup>28, 29, 30, 31</sup> There are even a few prescription drugs containing silver that are available, such as silver nitrate which is used to prevent conjunctivitis in newborns and to treat some skin conditions, and silver sulfadiazine which is used to treat burns.<sup>32</sup>

In addition to these uses, however, silver is now being looked at as a possible weapon against antibiotic-resistant bacteria. In 2005, BBC News reported that Robert Strohal, an associate professor at the Federal Academic Hospital in Austria, was studying the “effectiveness of a silver-impregnated dressing” and believed that such a dressing could “virtually eradicate the cross infection of MRSA in hospitals.”<sup>33</sup> An article published in a 2006 issue of the *Journal of the American Chemical Society* detailed a

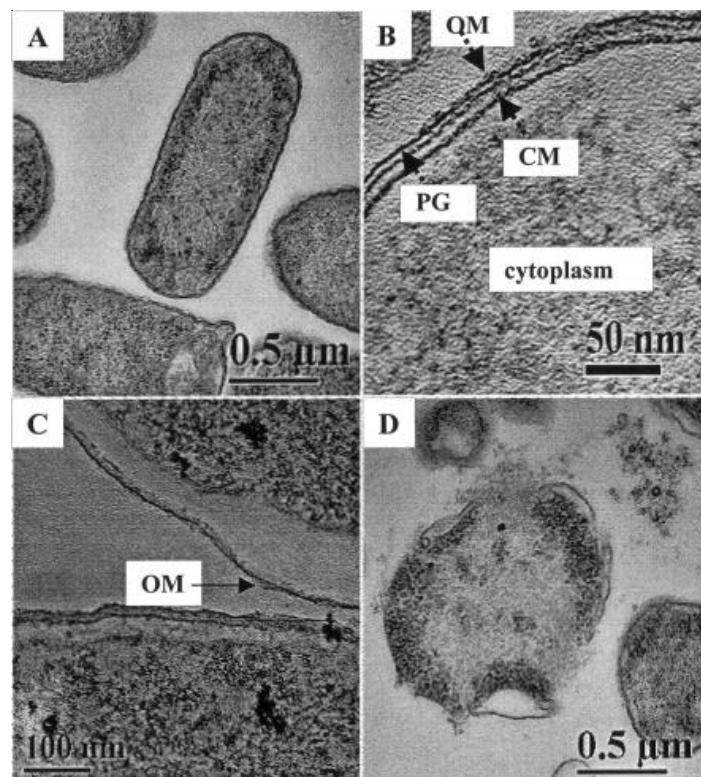


Fig. 5 Zero loss TEM images of an *E. coli* cell. (A) After reaction with a 0-ppb silver ion solution for 24 h. (B) Enlarged view of portion of panel A. (C) After reaction with a 900-ppb silver ion solution for 24 h. (D) Another *E. coli* cell after reaction with a 900-ppb silver ion solution for 24 h. OM, outer membrane; PG, peptidoglycan layer; CM, cytoplasmic membrane.

study done by Varun Sambhy, *et al.*, on antibacterial composites embedded with silver bromide nanoparticles which indicated that the composites are “useful as antimicrobial coatings in a wide variety of biomedical and general use applications.”<sup>34</sup> Another study, reported in *The Journal of Physical Chemistry B*, demonstrated the “high antimicrobial and bactericidal activity” of silver nanoparticles against multiresistant strains of bacteria, including MRSA.<sup>35</sup> A 2006 *Current Science* article outlined a study in which silver was combined with antibiotics to improve their performance in fighting resistant bacteria.<sup>36</sup> *The Journal of Physical Chemistry C* included a 2007 article on a study of silver nanoparticles that showed they were “very efficient toward destroying Gram negative bacteria *Escherichia coli*.”<sup>37</sup> (See Fig. 4 and Fig. 5) In 2007, BBC News reported on another study, conducted by Barts and The London NHS Trust, “to prove that silver can be used to clear MRSA on the skin and thus protect vulnerable patients.”<sup>38</sup> Two studies were detailed in *The Journal of Physical Chemistry C* in 2008 on the antibacterial activity of silver, one of them reporting that “the bacterial inhibition ratio reached up to 95% [even] at a low silver concentration.”<sup>39, 40</sup> And a 2008 issue of *Environmental Science and Technology* included a study on air filters coated with silver particles, concluding that they were “effective for the removal of bioaerosols by inhibition of the survival of microorganisms.” *Bacillus subtilis* and *Escherichia coli* “were completely inhibited” within 10 and 60 minutes, respectively.<sup>41</sup>

### Historical Opposition to Silver

Although the medical industry and the FDA initially accepted the antibacterial properties of silver, their attitudes changed after the introduction of antibiotics.<sup>42, 43, 44</sup> At the outset, this may have been due to an overzealousness regarding the exciting new frontier of pharmaceuticals, or it may have been due, in part, to business interests which could not capitalize on the traditional uses of silver. Whatever the cause, however, the shift in viewpoint can not be denied.

The FDA acknowledges that some “colloidal silver products were recognized as official articles in the *United States Pharmacopeia*...and the *National Formulary*,” most notably colloidal silver iodide, mild silver protein, and ammoniacal silver nitrate solution. However, according to the FDA, “none of these formerly recognized

colloidal silver preparations has been official...since 1975.”<sup>45</sup> In 1996, the FDA went on to issue a ruling proposal, stating that over-the-counter drug products containing colloidal silver ingredients for the treatment and/or prevention of disease are “not generally recognized as safe and effective and are misbranded.”<sup>46</sup> In 1999, a final ruling was released, claiming that “there is a lack of adequate data to establish general recognition of the safety and effectiveness of colloidal silver ingredients.”<sup>47</sup> As a result of this ruling, over-the-counter colloidal silver products are not to be labeled with claims that they treat or cure any disease, although this ruling does not directly “apply to products marketed as dietary supplements.”<sup>48</sup>

In reading the FDA proposal and the final ruling, two items of interest stand out, although they are notable due to their absence. Neither of the FDA documents addresses prescription drugs containing silver or the antibacterial properties of silver. It is true that, in this case, the FDA concerned itself with *over-the-counter* products. In their presentation of the history of colloidal silver products, however, they included pharmaceuticals (such as colloidal silver iodide), but only highlighted those that were no longer listed in the *United States Pharmacopeia* and the *National Formulary*. Their willingness to include these particular products should have extended to those that are currently approved by the FDA and used in the medical field, such as silver sulfadiazine and silver-infused wound dressings. Although this omission may have been only an oversight, it is possible that, by incorporating them, the FDA would have weakened its case against over-the-counter products.

The only mention of silver as an antibacterial is a reference in the proposal to an outdated use of “mild silver protein as an ophthalmic [inflammation of the eye] anti-infective” and to “products [improperly] labeled for numerous disease conditions,” including *staphylococcus* and *streptococcus* infections.<sup>49</sup> In the final ruling, the FDA summarized public comments that had been submitted concerning over-the-counter colloidal silver products. Two of the comments, one presented by an unnamed physician, made mention of the antibacterial properties of silver, but these were both dismissed by the FDA as inadequate support for the approval of colloidal silver.<sup>50</sup>

The major safety concern presented by the FDA proposal and final ruling on over-the-counter silver products was *argyria*, “a rare condition associated with chronic exposure to silver-containing products.” *Argyria* manifests as a



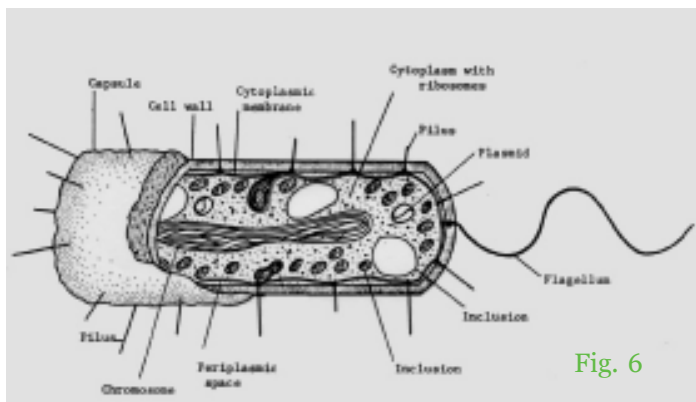
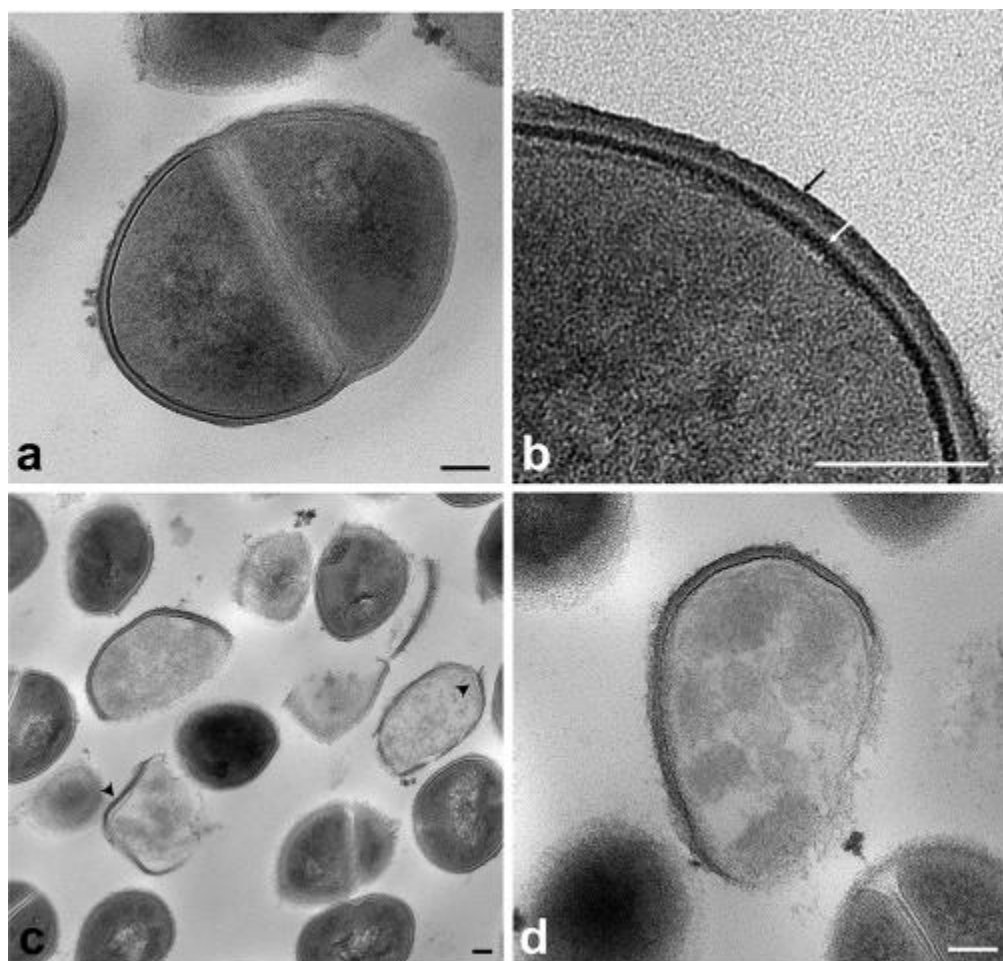


Fig. 6

“levels of silver exposure that have led to argyria in humans in the past are poorly documented.”<sup>54, 55</sup> Both the EPA and the CDC are convinced that silver is not a carcinogen for humans, and the CDC has reported that “no studies [have been] located regarding death in humans...after...exposure to silver or silver compounds.”<sup>56, 57</sup>

The concern of the FDA, when weighed against the additional information provided by the EPA and the CDC, does seem to be overstated, especially when the FDA does approve the use of some silver products. One of the more interesting examples of this bureaucratic discrimination involves the FDA approval of bandages infused with silver. In 2008, for example, the FDA approved the marketing of a bandage “constructed with silver ions that serve as antimicrobial agents.”<sup>58</sup> According

bluish-gray discoloration and is caused by a depositing of “silver granules in the skin, mucous membranes, and internal organs.”<sup>51</sup> The FDA mentioned a number of sources when questioning the safety of silver (*Argyria*, *The Pharmacology of Silver*, *The Pharmacological Basis of Therapeutics*; *Remington’s Pharmaceutical Sciences*; *The Dispensary of the United States of America*; and “Silver Products for Medical Indications: Risk-benefit Assessment,” an article that appeared in *Clinical Toxicology*), but the only adverse effect addressed by these sources, as quoted, was argyria. The *Annals of Occupational Hygiene* does agree with sources cited by the FDA concerning the “long-term...ingestion of soluble silver compounds or colloidal silver,” stating that it may cause argyria.<sup>52</sup> Argyria does seem to be the most serious adverse reaction to ingesting colloidal silver, and although it is irreversible, a person must be exposed to “high levels of silver for a long period of time...[and] it appears to be a cosmetic problem that may not be otherwise harmful to health.”<sup>53</sup> The EPA describes argyria as a “medically benign” condition, and the CDC has indicated that



Bar=100nm

Fig. 7 Internal structure of *Staphylococcus aureus* observed by TEM. (a and b) Untreated bacteria. (c and d) Bacteria treated with silver ion solution (0.2 ppm). Black and white arrows indicate peptidoglycan layer and cytoplasmic membrane, respectively. Note the separation of cell membrane from the cell wall (arrowheads).

to the pre-approval application letter, the manufacturer, Euromed, Inc., informed the FDA that the *Sureskin III Silver* bandage provides “an antimicrobial barrier to microbial colonization in the dressing.” Interestingly enough, this product was approved for both prescription and over-the-counter use.<sup>59</sup>

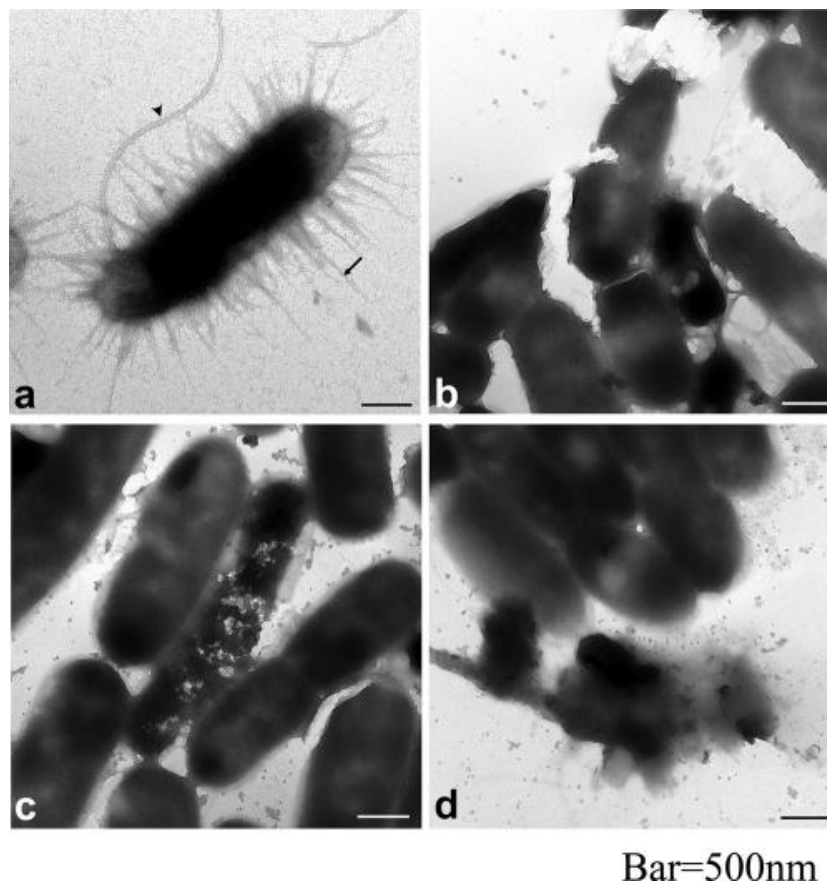
The 1999 FDA ruling specifically addressed over-the-counter colloidal silver products that were being marketed as drugs, but the FDA made no such ruling about colloidal silver that is marketed as a dietary supplement. According to the 1994 Dietary Supplement Health and Education Act (DSHEA), the FDA may immediately remove any dietary supplement from the market “if the FDA believes that it presents a public health hazard.”<sup>60</sup> This leaves one to wonder, then, whether the FDA’s decisions concerning colloidal silver has more to do with competition within the pharmaceutical market than any real concern about the purported safety issue of using a silver product.

### How Does Silver Work?

Traditionally, silver has been used in various applications for its antibacterial properties, but without a full understanding of how it functioned. Before discussing the antibacterial properties of silver, however, it is important to also understand the structure and function of bacterial cells. The structural components of a bacterial cell include “appendages (attachments to the cell surface) in the form of flagella and pili (or fimbriae); a cell envelope consisting of a capsule, cell wall and plasma membrane; and a cytoplasmic region that contains the cell chromosome (DNA) and ribosomes.” Flagella are protein structures

attached to the cell surface that make it possible for the cell to “swim in fluid environments.” Pili are “short, hair-like [protein] structures” that allow a bacterial cell to attach to other surfaces. The cell membrane is made up of several layers of material that protect the interior of the cell, transport substances into and out of the cell, and generate the energy required for the cell to function. The cytoplasmic region is the “genetic control center of the cell which determines all the properties and functions of the bacterium.”<sup>61</sup>

To fully appreciate the antibacterial function of silver, it is also necessary to explore the manner in which



**Fig. 8 External morphology of unstained *Escherichia coli* observed by TEM. (a) Untreated bacteria. An arrow and an arrowhead indicate fimbriae and a flagellum, respectively. (b, c, and d) Bacteria treated with silver ion solution (0.2 ppm).**

m a i n s t r e a m antibiotics work. There are two major mechanisms employed. The first is to interfere with cell wall development so that they are unable to connect to other cells and surfaces, and “since bacteria cannot regulate their internal pressure, bacterial cells...burst apart and die if [this] cross-linking [does] not occur.”<sup>62</sup> The second mechanism, which is more common among antibiotics, is to interrupt “a key biochemical process within bacterial cells.”

This is typically accomplished by an antibiotic entering the cell and “latching onto a key protein, hampering its function.”<sup>63</sup>

It is only in recent years that scientists have begun to unravel the bacteria-destroying functions of silver. A 2003 study by Yoshinobu Matsumura, *et al.*, demonstrated the “bactericidal activity of [the] silver ion” and indicated that

there may be two processes involved in its function. First, “bacterial cells...take in silver ion, which inhibits several functions in the [cells] and consequently damages [them].” The second process involves “the generation of reactive oxygen species [or oxygen radicals].” It is believed that these species are produced “through the inhibition of a respiratory enzyme” and that they actually attack the bacterial cells.<sup>4</sup>

A 2005 study by Mikihiro Yamanaka, *et al.*, corroborated the first of these hypothesized processes, observing that “the silver ion readily penetrates the interior of the cell,” but went on to indicate that “reactive oxygen species are primarily formed by a source outside the respiratory chain” and that additional “work is...necessary to clarify the involvement of oxygen in bactericidal actions of the silver ion.” The study further indicated that “bactericidal actions of the silver ion are caused primarily by its interaction with the cytoplasm in the interior of the cell.” The silver ion apparently penetrates a bacterial cell, without “causing damage to the cell membranes,” and then “denatures the ribosome and suppresses the expression of enzymes and proteins essential to ATP production.” The result is that the bacterial cell is “unable to sustain the membrane structures,” causing cell disruption.<sup>5</sup>

A 2008 study by Woo Kyung Jung, *et al.*, proposed that, “in addition to their effects on bacterial enzymes, silver ions caused marked inhibition of bacterial growth and were deposited in the vacuole and cell wall as granules.” Silver ions “inhibited cell division and damaged the cell envelope and contents of bacteria.” In the presence of silver ions, “bacterial cells increased in size” and exhibited structural abnormalities in “the cytoplasmic membrane, cytoplasmic contents, and outer cell layers.”<sup>6</sup> Bacterial cells, once penetrated by silver ions, are literally destroyed from the inside.

In addition to the processes mentioned above, it also appears that silver has the ability to bind “with cell’s DNA, preventing DNA from unwinding.” In 2004, Kareen Batarseh published a study in the *Journal of Antimicrobial Chemotherapy* and stated that “the effect of silver atoms on [the] unwinding of cellular DNA” inhibits the replication of bacteria and that the other mechanisms of silver may “work synergically” with this third process.<sup>7</sup>

## HISTORICAL CHRONOLOGY

- **8th Century:** Avicenna used silver filings to purify blood and to treat offensive breath and heart palpitations.
- **Middle Ages:** Silver plates and utensils used to fight disease.
- **18th Century:** Silver nitrate used to treat nervous system disorders, to treat ulcers, and to treat infections and burns.
- **1880’s:** Carl Credé started using silver nitrate to prevent bacterial conjunctivitis in newborns.
- **1861:** Thomas Graham coined the term “colloidal.”
- **1887:** Emil von Behring used silver nitrate to treat typhoid and anthrax.
- **1893:** Karl von Nägeli first identified the “oligodynamic effect” of metals.
- **20th Century:** In the early 20th Century, silver used in nose drops and sinusitis/common-cold remedies.
- **1910:** Henry Crookes discovered methods for preparing stable colloids.
- **1920:** Publication of A.B. Searle’s *The Use of Colloids in Health and Disease*.
- **1920’s:** FDA accepted colloidal silver as effective in treating wounds.
- **1928:** Penicillin discovered by Dr. Fleming.
- **1929:** By this date, it was possible to concentrate ionic silver into hydrosols.
- **1944:** First major report of penicillin-resistant *Staphylococcus aureus*.
- **1945:** Surgeon Generals declared that infectious diseases were no longer a threat.
- **1960’s:** Silver salts replaced colloidal silver as topical treatment for burns.
- **1970’s:** Silver compounds were introduced as topical treatment for burns.
- **1991:** Over 40% of *Staphylococcus aureus* strains were methicillin-resistant.
- **1994:** Office of Technology Assessment commissioned to study impacts of antibiotic-resistant bacteria.
- **1994:** DSHEA instituted.
- **1999:** FDA ruling against over-the-counter silver products.
- **1999:** Interagency Task Force on Antimicrobial Resistance created.
- **2005:** 94,000 patients developed invasive infections from MRSA.



### What Are the Benefits of Using Silver?

While the mechanisms of antibiotics and silver are somewhat similar in function, there may be additional benefits to choosing silver as an antibacterial agent. The most pressing issue at hand is the increasing regularity and severity of antibiotic-resistant bacteria. Bacteria continue to develop new ways to evade the actions of antibiotic drugs. “Many use pumps to rid themselves of antibiotics, while others launch search-and-destroy molecules into their surroundings, wiping out the drugs before they can [even] enter bacterial cells. Still others change the protein that the antibiotic targets so the antibiotic no longer binds to it.”<sup>8</sup> Ongoing studies on antibacterial properties of silver, however, indicate that silver is effective even against bacteria that are already antibiotic-resistant.<sup>9</sup>

Another benefit to using silver is that it does not appear to create the same amount of resistance in bacteria as traditional antibiotics. Ian Chopra, Professor of Microbiology at the University of Leeds, reported in a 2007 article in the *Journal of Antimicrobial Chemotherapy* that there are fewer than twenty published reports of silver resistance in bacteria “and only a few of these include data that help clarify resistance mechanisms.” Professor Chopra went on to indicate that “current evidence suggests the clinical threat [due to silver resistance] is low” because of the “multifaceted mode of action of the silver ion.”<sup>10</sup>

A third advantage to using silver concerns adverse reactions. In addition to the long-term effects of antibiotic resistance, there are “more immediate risks of antibiotic use.” Most adverse effects are “generally considered to be infrequent and mild”; however, there are an increasing number of “serious antibiotic-associated adverse events.” In a 2008 issue of *Clinical Infectious Disease*, Nadine Shehab, *et al.*, reported that each year over 142,000 emergency room visits occur because of antibiotic-related complications. The adverse reactions identified in this study ranged from a “mild allergic reaction” (dermatitis, drug eruption, erythema, flushing, localized edema, pruritus, rash, rash morbilliform, and urticaria) to a “moderate-to-severe allergic reaction” (anaphylaxis, angioedema, erythema multiforme, exfoliative dermatitis, facial-pharyngeal-genital edema, hypersensitivity vasculitis, red man syndrome, respiratory distress or arrest, serum sickness, and Stevens-Johnson syndrome).<sup>11</sup> Adverse reactions caused by silver, however, are rare, and those

that do occur are dependent on long-term exposure and the specific type of silver that is involved.

In addition to immediate adverse reactions, it is well established that the use of antibiotics disrupts the balance of intestinal flora. Antibiotics not only kill harmful bacteria—they also destroy beneficial bacteria.<sup>12, 13</sup> The beneficial flora synthesize and excrete vitamins, prevent colonization by pathogens, antagonize other bacteria, promote the development of certain tissues, and stimulate the production of natural antibodies.<sup>14</sup> When beneficial flora are destroyed by antibiotic use, these essential activities are disrupted, and harmful bacteria are allowed to flourish, causing subsequent infections like yeast and *Clostridium difficile* colitis. In fact, *Clostridium difficile* bacteria are “responsible for over 20,000 infections per year in the U.S.”<sup>15</sup> A recent study by Dr. David Relman, an infectious disease specialist at Stanford University and the Veteran Affairs Hospital at Palo Alto, has also indicated the amount of disruption caused by antibiotics is even more harmful and long-lasting than previously thought. Dr. Relman, *et al.*, tested the effects of ciprofloxacin, which is “believed to be among the least disruptive of [antibiotics].” During the study, they discovered that almost 30% of beneficial bacteria were disrupted and that the flora had still not recovered six months after the antibiotic course had been completed by the patients.<sup>16, 17</sup> While it is still not clear what effect silver has on beneficial bacteria, silver does appear to have the ability to destroy opportunistic organisms, such as *Candida albicans*.<sup>18</sup>

Another benefit of using silver involves white blood cells. It is well established that many antibiotics cause neutropenia (a severe reduction in white blood cell count), including penicillin.<sup>19, 20, 21, 22, 23</sup> This reduction actually inhibits the body’s natural immune responses. Silver, on the other hand, “will not interfere with normal white blood cell...activity” and may even enhance it.<sup>24</sup>

As research continues, there are exciting new uses for silver that are indicated. In addition to its antibacterial properties, silver is also being studied as an antifungal agent. A study published in *Mycoses* in 2007 indicated that silver is effective against four fungi “which cause major fungal infections in humans”: *Trichophyton rubrum*, *Candida albicans*, *Microsporium canis*, and *Aspergillus flavus*.<sup>25</sup> Silver has also been studied as an antiviral, and has been shown “to prevent [certain viruses] from being infective.”<sup>26</sup> In 2003, Eric Rentz published a retrospective study of silver as an antiviral in the *Journal of Nutritional &*



**Environmental Medicine**, indicating that silver may be a powerful weapon against SARS.<sup>27</sup> And in 2005, the *Journal of Nanobiotechnology* published a study in which J.L. Elechiguerra, *et al.*, claimed that silver is an effective treatment for the HIV-1 virus, able to “inhibit the virus from binding to host cells.”<sup>28</sup> Some researchers are even exploring silver’s use as a chemotherapeutic agent, claiming that it may be an alternative therapy to “the current cancer systemic therapeutic methods such as radiation, immunotherapy, chemotherapy, and antiangiogenic drugs” which have “many adverse side effects.”<sup>29</sup>

### Different Forms of Silver

Silver is a “naturally occurring element,” but it is used in a variety of forms in the health and nutritional industries.<sup>30</sup> There are two broad categories of distinct silver speciation (or type): 1) **silver salts and compounds**, and 2) **colloidal silver** (“insoluble silver particles suspended in water with or without other colloids or electrolytes”).<sup>31</sup>

### Silver Salts and Compounds

Silver nitrate is a “common natural substance,” although it can also be prepared by “dissolving elemental silver in...nitric acid.”<sup>32</sup> In the Middle Ages, silver nitrate was “used for the treatment of nervous disorders.”<sup>33</sup> During the 18<sup>th</sup> century, silver nitrate “was used in the treatment of ulcers.”<sup>34</sup> By the 19<sup>th</sup> Century, dilute solutions of silver nitrate were used to “treat infections and burns.”<sup>35</sup> In the 1880’s, a German obstetrician, Carl Credé, began using silver nitrate as an antiseptic treatment to prevent bacterial conjunctivitis in newborns.<sup>36</sup> This method became standard practice in obstetrics and is still used to this day.<sup>37</sup> In 1887, Emil von Behring (awarded the Nobel Prize in Physiology or Medicine, 1901) “used the same compound to treat typhoid and anthrax.”<sup>38</sup> Silver salts, including silver nitrate, have also “been used in treating...nicotine addiction, gastroenteritis, and infectious diseases, including syphilis and gonorrhea.”<sup>39</sup> By the early 20<sup>th</sup> Century, silver nitrate was also “used in nose drops [as well as] in sinusitis and common-cold remedies.”<sup>40</sup> During the 1960’s, silver salts (such as silver nitrate) began to replace colloidal silver and silver proteins as a topical treatment for burn wounds, and silver compounds (such as silver sulfadiazine) were introduced in the 1970’s.<sup>41, 42, 43</sup>

### Colloidal Silver

In 1861, Scottish chemist, Thomas Graham, coined the term “colloidal” to describe substances diffused into a solution. Metal colloids “are minute clusters of neutral metal atoms” and can be prepared either as “reductions of soluble silver salts” or by applying “direct current on a silver electrode in aqueous solution.”<sup>44</sup> These colloids, while recognized as a great scientific discovery, were seen by the medical industry as unreliable until methods for preparing stable colloids were discovered by Henry Crookes (son of the famous chemist and fellow of the Royal Society, Sir William Crookes) in 1910. These methods were described by A.B. Searle, a chemist and consultant to the Department of Scientific and Industrial Research of the British Association for the Advancement of Science, in his book, *The Use of Colloids in Health and Disease* (1920):

- a) Mechanically grinding a substance and fluid together.
- b) Dilution of a substance in liquid.
- c) Using electrodes of the substance immersed in liquid and passing electric current through them.
- d) Addition of a suitable electrolyte to a colloidal gel.

In his studies, Crookes discovered that certain metals (including silver), when in a colloidal state, have a powerful germicidal action, but are quite harmless to humans. Crookes tested silver against a number of bacteria and published his findings in *Lancet* in 1914.<sup>45</sup> Crookes’ conclusions were further studied by W.J. Simpson, Professor of Hygiene at King’s College, and R. Tanner Hewlett, Professor of Bacteriology at the University of London. Simpson and Hewlett tested the germicidal action of colloidal silver on the typhoid bacillus. They noted in *Lancet* that “there can be no doubt...that colloidal silver in the form of collosol [colloidal silver in the form of a liquid] is an active germicide...[and] that the collosols are non-poisonous and have been administered internally.”<sup>46</sup>

Starting in the 1920’s, the FDA accepted colloidal silver “as being [an] effective [treatment] for wound management.”<sup>47</sup> These colloidal solutions became the “most common delivery system” of silver and were used until 1960, when silver proteins (which are also colloidal) became a more popular form. The colloidal solutions contained “charged pure silver particles (3-5 ppm)” held in suspension by a small electric current, and they were

applied topically to burn wounds.<sup>48</sup> Silver proteins were also used as a topical treatment for burns.<sup>49</sup> These are prepared by mixing silver nitrate, sodium hydroxide, and proteins (usually gelatin, but other types of proteins are also used). Once this complex colloidal aggregate is formed, it “can be diluted with water to the desired concentration” and be used as a topical bacteriostatic disinfectant.<sup>50</sup>

### **Ionic Silver**

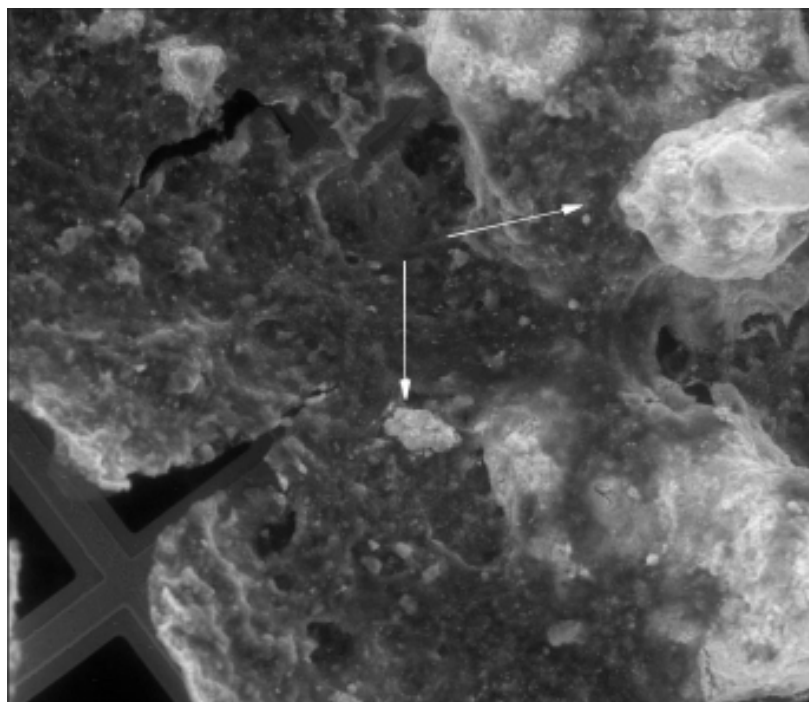
Ionic silver, although technically a colloidal, does seem to offer more beneficial properties than the traditional colloidal silver. Ionic silver “can be generated by electrolyzing the silver metal or dissolving...silver compounds” and appears to have superior antimicrobial activity.<sup>51</sup> One of the reasons for this, in addition to the charge of the particles, might be that “silver ions in solution offer a greater surface area because of the fact that they are individual atoms, not clusters of atoms as seen in a colloid.” This means that “they react more quickly and readily,” and since they “are relatively smaller than colloidal particles, they will penetrate...more rapidly and effectively.”<sup>52</sup> Eric Rentz, in a 2003 article in the *Journal of Nutritional & Environmental Medicine*, points out that “the smaller the *colloidal* silver particle, the more biologically active it becomes....The activity...is directly proportional to the absorption power upon a biological surface, which totally depends upon the surface area of the metal.”<sup>53</sup> Some of the earliest work on the ionic nature of liquid solutions was done by Svante Arrhenius (awarded the Nobel Prize in Chemistry in 1903) during the 1880’s. He proposed that charged particles in a solution will conduct electricity and carry the chemical activity of the particles.<sup>54</sup> In 1893, Swiss botanist Karl von Nägeli “first identified the oligodynamic effect...to best describe how extremely low metal ion concentrations beyond definitive chemical analysis exert potent biocidal actions.” He determined that silver was “an effective biocide” at very minute concentrations.<sup>55, 56</sup> By 1929, it was possible to concentrate ionic silver “into electrolytic suspensions (called silver hydrosols).”<sup>57</sup>

### **Additional Forms of Silver**

In more recent years, two additional forms of silver have been introduced to the medical field. One is a “binary alloy of silver...and oxygen” that is used to coat a high density polyethylene mesh and incorporated in gauze wound dressings.<sup>58, 59</sup> The other is nanosilver. Nanosilver is technically a nanoparticle of silver that measures between 1 and 100 nanometers (a nanometer is one-billionth of a meter). Nanotechnology makes it possible to imbue these tiny particles of silver in wound dressings and textiles or to create “antimicrobial coatings in a wide variety of biomedical...applications.”<sup>60, 61</sup> As with other applications of silver, nanosilver also exhibits antibacterial properties.<sup>62, 63, 64</sup>

### **The Importance of Silver Speciation and the Oligodynamic Effect**

It is true that “many of the previous therapeutic uses of silver have been abandoned,” including oral, intravenous, intramuscular, and subcutaneous administrations; however, “topical medicinal products” are still used, and many people ingest colloidal silver remedies that are marketed as dietary supplements.<sup>65, 66</sup> The primary distinction between the medical and



**Fig. 9** The microscopic image above shows silver nanoparticles attaching themselves to bacteria.

nutritional industries' use of silver seems to be one of application. While the medical industry once employed silver in both topical and internal applications, in more recent years they have chosen to limit the use of silver to topical. The nutritional industry, however, has continued to recommend both.

As has already been noted, the FDA's major concern with over-the-counter colloidal silver products is the possible side effect of argyria. However, in discussing the uses and effects of silver, it is important to first address the issue of speciation (or type). Speciation is an important issue when "discussing both the benefits and the toxicities of silver-based drugs," and it is also essential for a proper understanding of "colloidal silver preparations in general."<sup>67</sup> *Speciation* refers to "the physical and chemical properties of a metal as it relates to the metal's fate, transport, and toxicity." As already indicated, the two different speciations (types) of silver are: 1) **silver salts and compounds**, and 2) **colloidal silver**, and the "specific means used to create a given silver formula [will determine] its oligodynamic qualities."<sup>68</sup>

The term *oligodynamic*, coined by the Swiss botanist Karl von Nägeli, refers to a metal's ability to be effective in small traces. The speciation of silver will establish what sort of effect will be present, and there are three factors governing this oligodynamic action: 1) particle concentration, 2) particle size, and 3) particle charge.<sup>69</sup>

### Particle Concentration

Because of the oligodynamic effect of metals, only small concentrations of silver particles need be present for the silver to have an effect. Nägeli determined that "extremely low metal ion concentrations [of oligodynamic  $\text{Ag}^+$  (9.2 ppb to 5.5 ppm)]... exert potent biocidal actions." A 1970 Nasa-sponsored study confirmed Nägeli's findings using concentrations of 50 ppm and 250 ppb.<sup>70</sup> This has also been established by modern studies. Pavel Dibrov, *et al.*, stated in ***Antimicrobial Agents and Chemotherapy***, in 2002, that "the controversy over the mechanism of the bactericidal activity of low concentrations of  $\text{Ag}^+$  ions has been clarified" after showing that low concentrations [micromolar, 1/1,000,000 (one millionth) molecular weight per liter (mol/L)] of silver were able to "induce a massive proton leakage through [a] *Vibrio cholerae* membrane," resulting in complete deenergization of the cell.<sup>71</sup>

### Particle Size

The definition of *oligodynamic* indicates that silver particles do not need to be large in order to have an impact. In fact, there are strong links between large particle size and toxic effects, like argyria.<sup>72</sup> The size of the particles in a given speciation of silver is very important since the "activity... is [also] directly proportional to the absorption power upon a biological surface," and this is totally dependent on the surface area of the metal. Colloids are made up of smaller particles than compounds, which gives colloids the "ability to absorb and penetrate into the greatest possible biological area in the lowest possible effective dose," and "the smaller the *colloidal* silver particle, the more biologically active it becomes."<sup>73, 74</sup> In the last century, silver products typically contained particles that were 14-26 nm in size; however, in recent years, technology has made it possible to reduce the size of silver particles to 0.8 nm.<sup>75</sup>

### Particle Charge

The term *oligodynamic* only applies to "charged silver particles," or ions ( $\text{Ag}^+$ ).<sup>76</sup> Neutral silver (Ag) does not have the microcidal nature that silver does in the ionic state. The charge of the ion is necessary in facilitating electron displacement in microbes. It is the charge that "effectively yanks electrons away from a molecule... weakening the molecular bond and rendering it susceptible." In his retrospective study of silver, published in the ***Journal of Nutritional & Environmental Medicine***, Eric Rentz indicates that microbial cells "selectively bond only with  $\text{Ag}^+$ ."<sup>77</sup>

It is important to note that most of the beneficial aspects of silver seem to be "determined by... the silver speciation content of oligodynamic silver ions [ $\text{Ag}^+$ ]," whereas all of the toxicity of silver is related specifically to "the non-oligodynamic silver content *plus* (c) the specific anion [negatively charged ion] attached."<sup>78</sup> Toxic effects related to the non-oligodynamic forms (silver salts and compounds) include decreased blood pressure, diarrhea, stomach irritation, decreased respiration, fatty degeneration of the liver and kidneys, changes in blood cells, and argyria.<sup>79</sup> However, the safety of oligodynamic silver ( $\text{Ag}^+$ ) is firmly established: it "is not... toxic to the immune, cardiovascular, nervous, or reproductive systems [and it] is not considered to be carcinogenic." On the



contrary,  $\text{Ag}^+$  manifests all of the therapeutic benefits that have been historically established for silver.<sup>80, 81, 82</sup>

The toxicities noted above are directly connected with silver products that contain “reduced or neutral silver [which] has no known medical value.” These include silver salts, silver compounds, and colloids that are created without ions. These products will still provide some benefit if there are silver ions present, but most of them “have difficulty achieving biologically meaningful concentrations of  $\text{Ag}^+$ .” Ionic (colloidal) solutions, however, can concentrate  $\text{Ag}^+$  into electrolytic suspensions.<sup>83</sup>

The importance of this must not be overlooked. The fears expressed by the FDA concerning the toxic effects of silver can only apply to those products that contain non-oligodynamic forms of silver, not those that are ionic ( $\text{Ag}^+$ ).

### Concluding Thoughts

Although silver has been used for thousands of years as an antimicrobial agent, during the last century there have been a number of suspicions raised about its effectiveness and safety. These concerns, however, have not taken into account the speciations of silver or the oligodynamic actions of this noble metal. The most current research indicates that a silver product must have a *low* silver concentration and contain *small* silver particles that are *charged* (ions) for it to produce the most beneficial effects.

NutriLink is pleased to introduce a safe silver alternative that is produced through proprietary processes. The result of this improved nanotechnology is a non-colloidal, water soluble silver that is more effective in transporting silver ions through cells, and it is easily eliminated from the body, rather than collecting in the skin and tissues. NutriLink’s ionic silver provides a clear mineral water solution of silver ions in concentrations of not less than 25 parts per million (**Silver Force™**) and in a super strength version of 100 parts per million (**Super Silver<sup>100</sup>**). The process used to produce this ionic silver eliminates the relatively large micron-sized colloidal silver particles floating in water and, instead, bonds angstrom-size clusters of silver atoms ionically to the water molecules themselves. With this process, wherever water penetrates the cells and tissues, silver ions penetrate as well.

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