

***Serratia marcescens*: a historical perspective**

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Serratia marcescens (“*S.mar*”), a member of the Enterobacteriaceae order of bacteria, is a ubiquitous gram-negative bacillus found in soil, water, and plants. It is a facultative anaerobe (can exist with or without oxygen) which thrives in damp environments and sometimes produces a bright red pigment named prodigiosin. This pigment results in relatively easy identification of this bacterium in culture media, a helpful feature which accounts for its popularity as a tracer organism in a variety of bacterial experiments.

S. mar has a high affinity for starchy substances like bread and polenta, to which it occasionally imparts a disturbingly bloody appearance. Recorded instances of this (presumably *S. mar*-related) phenomenon date as far back as 323 B.C., during Alexander the Great’s siege of the city of Tyre, an island fortress off the coast of present-day Lebanon. A soldier breaking bread thought that the inner aspect looked bloody. Aristander, one of the seers accompanying the Macedonian army, interpreted this finding as a good omen signifying the fall of Tyre, as blood on the bread’s surface would surely have meant defeat for the Macedonians. The hitherto dispirited troops rallied, and shortly thereafter broke through Tyre’s South Harbor and captured the city.

In 1169 in Alsenin, Denmark, a priest saw what appeared to be blood on a Communion wafer (the “Host”). The terrified priest reported his finding to his superiors, who predicted that blood would soon be shed by Christians. Two weeks later, a Slovenian army invaded the area and laid waste to the town and its inhabitants.

In 1263 in Bolsena, Italy, the “Miracle of Bolsena” is said to have occurred. A priest named Peter of Prague was celebrating mass at St. Christina’s church in Bolsena, when he noticed what he thought was blood on his robe and on the altar linen (“Corporal”) just after the consecration prayer over the Communion wafers. Convinced that the doctrine of transubstantiation¹ had just been enacted before his eyes, the distraught priest contacted Pope Urban IV, who was residing in the nearby town of Orvieto. The pope conducted an investigation, verified the priest’s findings, and had the Host and Corporal transferred to Orvieto. He instituted a new Feast of Corpus Christi the following year and authorized

construction of a new Cathedral of Orvieto, which prominently displays the Corporal to this day.² The Renaissance artist Raphael commemorated the story (whether fact or fiction) of the Mass at Bolsena with a 1512 fresco painted at the Vatican palace.

In 1383 in Brandenburg, Germany, a knight named Heinrich von Bulow had a quarrel with the Bishop of Havelberg. Von Bulow proceeded to burn down the church and much of Wilsnack, one of the bishopric's villages. One week later, after a night of heavy rain, parishioners examining what was left of their church found 3 intact consecrated wafers with the appearance of blood on their surfaces ("The Holy Blood of Wilsnack"). A miracle was deemed to have occurred, and for the next 180 years pilgrimages were made to the church in Wilsnack.

The darkest side of the bleeding Host story is typified by events which are said to have occurred in Sternberg, Germany in 1492 (there are numerous versions of this story). An unscrupulous priest named Peter Dane allegedly gave 2 sacramental wafers which he himself had consecrated to a Jewish pawn-broker to release some pawned goods. According to one version of this tale, the wafers were stabbed in an occult Jewish ritual, resulting in such profuse bleeding that the pawn broker's frightened wife returned the wafers to Peter Dane. He responded by taking steps to have the 27 Jews allegedly involved in the profanation of the Host burned at the stake on Oct 24, 1492. This episode typifies the allegations of desecration of the Host in Europe in the middle ages that were pretexts for extreme anti-Semitic acts, including expulsions and executions.

In August, 1819, during a very wet summer, red spots started appearing on polenta, bread, rice and other starchy foodstuff in the home of a peasant near Padua, Italy. This phenomenon soon spread to other cities and to more than 100 households. Many explanations were offered, including the assertion that the wrath of God was causing the polenta to bleed because it was made from the cornmeal which had been hoarded 2 years earlier during a famine. Public fear and uproar were such that a commission consisting of police, health professionals, and university officials was formed to investigate matters. One member of the commission was Bartolomeo Bizio, a pharmacist and student at the University of Padua. Bizio independently conducted a series of experiments using "bloody" polenta separated by a distance from fresh polenta under a bell jar, altering temperature, humidity and other variables. Under humid conditions, the red discoloration always appeared on the surface of the fresh polenta within 24 hrs and then spread to involve the entire piece of polenta. Based on his experimental observations, and with the use of a rudimentary microscope, he

concluded that the so-called bleeding polenta was a natural (as opposed to supernatural) process caused by a micro-organism which he mistakenly believed was a fungus. He named the organism *Serratia marcescens*. *Serratia* was derived from the name of the Italian physicist Serafino Serrati, who had invented a steam engine that powered the first steamboat on the Arno River in 1787, 20 years ahead of Robert Fulton. *Marcescens* is the Latin word for decaying, which refers to the integrity of the starchy substance as the infection with the micro-organism progresses.

Because of the ease of identifying pigmented *S.mar* in culture, and because *S. mar* was long regarded as completely innocuous with respect to human pathogenicity, it became a very useful tracer micro-organism for studying the spread of bacteria. Several examples of its use during the first half of the 20th century are as follows. In 1906, after an outbreak of influenza among members of Parliament in London, a M.H. Gordon was commissioned to study atmospheric hygiene in the House of Commons. After gargling with a solution of *S.mar*, he loudly recited passages from Shakespeare to an audience of empty agar plates. Characteristic red colonies grew on plates nearby as well as at a distance, showing that, in addition to coughing and sneezing, loud talking is capable of spreading bacteria³. In the 1930s and 1940s, several experiments were performed using *S.mar* painted on the base of teeth and surrounding gums of patients about to undergo dental extraction^{4,5}. Blood cultures were taken post-extraction, and in a sizable minority of pts (20% average of 2 sets of experiments⁴, 41% in another experiment⁵), *S.mar* was recovered, demonstrating that bacteremia occurs not infrequently after dental extraction. None of the patients experienced side effects. In 1957, as reported in the *New England Journal of Medicine*⁶, *S.mar* was painted on the periurethral mucosa of 3 semi-comatose patients with indwelling Foley catheters. After a lag of 3 days, heavy growth of *S.mar* was noted in the urine of all 3 patients, suggesting that the presence of an indwelling urinary catheter predisposes to the entry of bacteria into the urinary tract.

In approximately the middle of the 20th century, reports of significant infections by *S. mar* began to challenge the long-held view that this bacterium was innocuous⁷. In 1951, 11 cases of *S.mar* urinary tract infections, including some bacteremias and 1 endocarditis-related fatality, were reported to have occurred over a 6-month period at Stanford University Hospital⁸.

In 1966, 8 cases of *S.mar* infections, mostly of the urinary tract, were reported to have occurred over a 3-month period in the nursery at the University of Virginia Hospital in Charlottesville, VA.⁹ Umbilical cultures of newborns in that nursery showed a 64.5% colonization rate. The probable source was tracked to plastic bottle caps on sterile saline containers. In 1976, 210 cases (including 8 fatalities) of infections by a single, multiply drug-resistant strain of *S.mar* were reported to have occurred over a 21-month period at 4 Vanderbilt University teaching hospitals. Hand-to-hand transmission by medical and nursing personnel who rotated through the hospitals was believed to be the principal mode of spread¹⁰.

By the 1970s, *S.mar* had been implicated in virtually every type of infection, and its pathogenicity in humans could no longer be denied. It is an opportunistic organism which produces nosocomial infections almost exclusively. It shows a high rate of antibiotic resistance. The typical setting is that of a bed-ridden, hospitalized patient who may have received broad-spectrum antibiotics and has an indwelling urinary catheter. Predisposing medical procedures include bronchoscopy, cystoscopy, peritoneal or hemodialysis, and placement of indwelling vascular catheters.

Perhaps the most controversial use of *S.mar* in modern times was as a tracer organism in biological warfare experiments conducted by the U.S. military. In a November, 1976 article in the Long Island newspaper *Newsday*, it was revealed that the U.S. government had secretly conducted population vulnerability and bacterial viability studies in San Francisco and New York in 1950. In San Francisco, the Navy had released *S.mar* into the water off the coast. The waves and wind aerosolized the bacteria, which were carried inland and captured at monitoring stations. The question was raised as to whether the use of *Serratia* by the Navy might have caused the 11 *S.mar* infections reported at Stanford University Hospital in 1951. So vigorous was the public reaction to this article that Senate hearings on biologic testing were held in March and May of 1977¹¹. It was disclosed that government testing with *S.mar* had been performed at least 29 times at a variety of government and military locations and 7 times in civilian population areas between 1949 and 1968. Sen. Richard Schweiker of Pennsylvania went on the attack at the hearings, grilling the military brass present on why experiments with *S.mar* were being conducted by the military long after it became aware of at least the potential for significant infection in humans in 1951. The beleaguered Brigadier General William Augerson was in the awkward position of trying to answer questions about decisions made by others 25 years earlier. He candidly admitted that, in 1951, *S.mar* was

considered a totally innocent bacterium. He also pointed out that the San Francisco experiment was conducted by the Navy, and he himself was an Army man. Other issues raised included the lack of transparency in the experiments; the total absence of informed consent; and the lack of any monitoring of the civilian population at risk for possible adverse health effects, specifically in the Navy experiment off San Francisco. Fortunately for all concerned, the *Serratia* species used by the military in its vulnerability and other studies over the years was never conclusively linked to well-documented human infection. Material from the Stanford University infections was never archived, so the Stanford strain(s) could not be compared with the strain used by the Navy. It was pointed out that all 11 patients at Stanford had pre-existing urinary tract abnormalities and that most had indwelling catheters, a setting not dissimilar to that seen with other nosocomial outbreaks of *S.mar*.

Three months after the Senate hearings, J.J.Farmer and others from the CDC reported on their review of the serotypes of all 100 *S.mar* outbreaks in the USA between 1950 and 1977¹². Not a single serotype matched the strain of *S.mar* used in the government's vulnerability studies. The offensive bioweapons program of the U.S. was terminated in 1969 by executive order of President Richard Nixon. Testing of biological agents for defensive purposes was permitted and may well be ongoing, but it would be under much more stringent control than a half century ago.

References

1. Christian doctrine which asserts that, during Mass, the Communion bread and wine become the body and blood of Christ.
2. The veracity of the story of the Miracle of Bolsena is very much in doubt. Pope Urban IV makes no mention of it in his bull establishing the feast of Corpus Christi, and neither do 2 biographers, contemporary with Urban IV, who were chroniclers of his time in Orvieto.
3. Anonymous. 1969. *Serratia septicaemia*. Br. Med. J. 4:756–757

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6. Kass E. H., Schneiderman L. J. 1957. Entry of bacteria into the urinary tracts of patients with indwelling catheters. *N. Engl. J. Med.* **256**:556–557
7. In 1958, the case of the “Red Diaper Syndrome” was reported (Waisman H. A., Stone W. H. 1958. The presence of *Serratia marcescens* as the predominating organism in the intestinal tract of the newborn. *Pediatrics* **21**:8–12). This case does not illustrate the human pathogenicity of *S.mar*, but because it is mentioned in virtually every review of *S.mar*, it is included in the present article. The diapers of the infant of a geneticist at the University of Wisconsin were supplied by a commercial diaper service. Several days after they were washed and placed in a receptacle awaiting pick-up, they developed a red discoloration that the diaper service was unable to launder away. The father, being aware of the “Blue Diaper Syndrome”, a disorder of tryptophan metabolism, suspected an inborn error of metabolism. An extensive evaluation followed. The red diaper discoloration was found not to be hemoglobin or anything in the infant’s food. Her stool culture showed heavy growth of pigment-producing *S.mar* with spectral characteristics identical to the red discoloration of her diapers. The totally asymptomatic infant was placed on sulfasuxidine, and over the course of 9 months, her stool gradually became populated with normal gut flora and the *S.mar* disappeared. It was subsequently learned that research into aerosolization techniques was being conducted in a building less than 500 yards away from the hospital, and that the tracer organism being used and emitted into the air was a strain of *S.mar* with identical antigenic characteristics to the strain identified in the infant’s stool. In a slightly tongue-in-cheek summation of events years later in a *Lancet* Letter to the Editor, J.J.Farmer of the CDC says: “Fortunately, at 9 months the child was no longer colonised, much to the relief of the parents, the laundry, and the scientist who was in charge of the aerosol project”.¹²

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