SERRATIA MARCESCENS is a bacterium recognized with increasing frequency as a cause of serious infection in man. This micro-organism has a romantic history dating to antiquity, when, because of production of a red pigment, it masqueraded as blood. In this century, this distinctive pigmentation, combined with its apparent low level of virulence, led to its use as a biologic marker. This article will review the more distinctive historical aspects of S. marcescens and discuss its clinical status as an emerging pathogen.

BACTERIOLOGY

Serratia marcescens is an aerobic, motile, gram-negative bacillus classified as a member of the division klebsiella-enterobacter-serratia, within the family enterobacteriaceae. Some strains of S. marcescens are capable of producing pigment, the intensity of which ranges from dark red to pale pink, depending on the age of the colonies. The pigment can be present after incubation at room temperature but usually disappears after subculturing. The pigment was extracted by Kroft in 1902 and named “prodiogenin”; however, it was not until 1960 that its structure was elucidated by Rapoport and Holden. Although the pigment is insoluble in water, attempts to exploit it as a commercial dye failed because of its sensitivity to light.

The organism has been isolated from water, soil, sewage, foodstuffs and animals. It may flourish in reptiles and is known to cause disease in rabbits, horses, deer and water buffalo. Under experimental conditions, it is pathogenic for mice, rats, guinea pigs, hamsters, turtles and dogs.

Until the 1950’s S. marcescens was generally considered a harmless saprophyte. One hospital survey of klebsiella-enterobacter-serratia infection in 1964 listed only three infections attributable to S. marcescens. Although only 15 cases of serratia bacteremia had been recorded in the medical literature by 1968, it was reported that only 3 cases of serratia bacteremia in one hospital alone from 1968 to 1977. The organism has now been implicated as an etiologic agent in every conceivable kind of infection, including those of the respiratory tract (lung abscess, bronchietasis, pneumonia and empyema) and urinary tract. Meningitis, otitis media, peritonitis, endocarditis, infections of the musculoskeletal system (septic arthritis and osteomyelitis), wounds and eyes, lymphadenitis and infections of the skin.

MASQUERADE OF BLOOD

Serratia marcescens has a predilection for growth on foodstuffs, especially the starchy variety, where the pigmented colonies are easily mistaken for drops of blood. As early as the sixth century B.C. Pythagoras had noted the appearance of a bloody coloration on foodstuffs, and in the 1800’s Ehrenberg uncovered the red blood cells in the aquarium. The first account by classical historians of the appearance of blood on foodstuffs was recorded in 332 B.C. at the siege of Tyre in Phoenicia (modern Lebanon). There, the Macedonian army of Alexander the Great took inspiration from an omen—drops of blood trickling out of the soldiers’ bread. The Macedonian seers interpreted this dramatic event as prophesying the destruction of Tyre and rallied the previously dispirited army to victory. Tyre was eventually stormed and left in ruins.

Gaughan uncovered more than 35 historical reports of blood flowing from Eucharistic bread, the Host; the first such incident was recorded in 1169 in Denmark. The starchy sacrament incubated in the damp environment of medieval churches provided an excellent substrate for the growth of S. marcescens. Since the Eucharistic bread symbolized conversion into the body of Christ, the appearance of blood on the Eucharistic bread represented a dramatic testament to this dogma. In 1264, a priest in Bolsena, Italy, who allegedly doubted the miraculous view of the sacrament was celebrating mass when “blood” appeared on the Eucharistic bread and dripped onto his robe. This episode was commemorated by Raphael in his fresco “The Mass of Bolsena.”

Unfortunately, many of these episodes also served as a basis for the persecution of Jews who allegedly stabbed the Host, and Scheuren has observed that, with the religious fanaticism of those times, this saprophyte contributed to the death of more people than many pathogenic bacteria.

From the Division of Infectious Diseases, Department of Medicine, University of Pittsburgh School of Medicine, and the Veterans Administration Medical Center (address reprint requests to Dr. Yu at the Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261).

*The research of Ehrenberg remains the definitive work on this subject, although reviews by Heffner and Gaughan may be more accessible.
Not until 1819 was the source of this miraculous blood attributed to a microorganism. At that time, a bloody discoloration of a cornmeal mush called polenta was observed in an Italian peasant’s home. The household not only became distraught by this mysterious visitation but also became fearful of divine vengeance, as predicted by the crowds who flocked to their home. Rumors spread that a supernatural power had caused blood to spring from the polenta because it had been made from cornmeal that had been hoarded and denied the hungry during the famine of 1817. Bartolomeo Bizio, a young pharmacist, demonstrated that the “blood” was caused by a living organism, which he mistakenly believed was a fungus. He named this organism *Serratia marcescens*. *Serratia* was named in honor of an Italian physician, Serafino Serrati, who Bizio thought had been slighted in favor of American inventors as to priority for the invention of the steamboat. *Marcescens* is derived from the Latin word “to decay” since Bizio observed that the pigment deteriorated quickly, dissolving from a light-pink material into a purplish-red, viscous form. Bizio’s experiments were of historical interest because they were one of the earliest instances of the use of solid medium (in this case, cornmeal mush) for the cultivation of chromogenic bacteria. Vincenzo Sette, an Italian physician who also concluded that the red coloration originated from a microorganism, dispelled much of the mysticism generated by the superstitious populace. By reproducing the reddening of polenta in the house of a priest, he disproved the notion that such an event could occur only in the house of a sinner.

In 1848, Ehrenberg named the organism *Mona prodigiosa*, or the “miracle bacterium,” which was later modified to *Bacillus prodigiosus*. By the 1920s, revisions in the taxonomy of bacteria as well as the desire to recognize the work of Bizio led to the gradual adoption of the name originally proposed by Bizio. In the bacterial nomenclature, *Serratia marcescens* is now out-ranked in age only by the genera *Vibrio* (1773) and *Polyangium* (1809).

The first clinical report involving *S. marcescens* was also a result of its pigment production. In 1913, Woodward and Clarke described a patient with bronchiectasis who had repeated episodes of what the patient considered to be blood-tinged sputum. However, microscopical examination failed to reveal red blood cells but did show large numbers of gram-negative bacteria, which proved to be *S. marcescens*. By 1957, similar cases were reported, and Robinson and Woolley coined the term “pseudo-hemoptysis” for this syndrome.

In 1938, Waisman and Stone reported the “occurrence of the red diaper syndrome” in an infant at the University of Wisconsin Hospital. Since the “blue diaper syndrome” is caused by the abnormal metabolism of tryptophan, the father of the infant, a genetics professor, suspected an inborn error of metabolism. Eventually, these workers isolated *S. marcescens* from the infant’s stool; absorption spectrophotometry verified that the coloration in the diapers originated from the pigment produced by the bacterium. They subsequently discovered that a pigmented strain of *S. marcescens* was being used as a marker in a study of aerosol techniques in a nearby laboratory and that it was antigenically identical to the infant’s strain. The infant was asymptomatic, but, despite sulfasuxidine therapy, his diapers continued to show red coloration for the next seven months.

**USE AS A BIOLOGIC MARKER**

With the present appreciation of the pathogenic potential of this organism, it is difficult to realize how benign it was once considered to be, and how recently. Indeed, its main claim to fame before its reputation as a nosocomial pathogen was its use as a biologic indicator.

In 1906 M. H. Gordon, after gargling a liquid culture of *S. marcescens*, recited passages from Shakespeare to an audience of agar plates in an empty House of Commons. He had been commissioned to study the atmospheric hygiene of the House after an epidemic of influenza had appeared among its members. Gordon recovered colonies of pigmented *S. marcescens* from agar plates, demonstrating that speech, as well as coughing and sneezing, could project bacteria into the air. He reportedly suffered no ill effects from the experiment.

As recently as the early 1970s, microbiology students rubbed their hands with suspensions of *S. marcescens* to demonstrate dispersal of bacteria by handshaking in routine laboratory exercises. The organism was even sprayed into hospitals to study bacterial drift and settling.

As a result of its use as a biologic marker, *S. marcescens* played an important part in many classic experiments, leading to an improved understanding of mechanisms of infection in man. In a controlled experiment conducted in 1920 to test the hypothesis that respiratory-tract infections could be transmitted by hand, Cumming sprayed the throats, mouths and lips of American soldiers with a suspension of *S. marcescens*. He subsequently isolated the organism from the hand, mess-kit utensils and oral cavities of other non-infected soldiers.

The knowledge that bacteremia can occur after dental extraction can be partially ascribed to the use of *S. marcescens* as a marker. In two classic studies, the organism was painted on the gum or neck of the tooth to be extracted, and blood cultures were obtained after tooth extraction. In one study, McEntaggart and Porterfield isolated *S. marcescens* from the blood of 41 per cent of their patients. None of the subjects were known to have suffered any ill effects.

Kass and Schneiderman documented the entry of organisms into urinary tracts via indwelling bladder catheters by applying *S. marcescens* to the urethra...
epithelium of three patients with indwelling catheters. Within three days, they recovered large amounts of the test organism from the urine of their patients. As recently as 1961, Laurenzi et al. applied *S. marcescens* to the mouth and pharynx of patients with respiratory-tract infections for use as a marker of contamination of sputum by mouth flora.

The most controversial use of *S. marcescens* as a biologic marker involved aerosolization experiments conducted by the United States Army to study the vulnerability of the United States population to germ-warfare techniques. In 1950 and 1952, Navy ships released *S. marcescens* into the ocean, where the organism became aerosolized by ocean waves and was then blown inland to San Francisco. Monitoring stations isolated the organism from the air as far as 80 miles inland. Public interest regarding the Army experiments was ignited by news reports in December, 1976, that a San Francisco hospital had experienced an outbreak of *S. marcescens* infections coinciding with the aerosolization experiments that had been performed in 1950. Wheat et al. had reported 11 cases of urinary-tract infection at Stanford University Hospital (San Francisco) in 1951, with one patient dying of the first known case of serrata endocarditis. In the same year, when *S. marcescens* was used covertly in aerosolization experiments in Calhoun County, Alabama, and Key West, Florida, the number of reported cases of pneumonia reached record peaks in those counties.

As a result of these disclosures, public hearings concerning biologic testing in the public domain were conducted in 1977 by the United States Senate Subcommittee on Health and Scientific Research. Of concern to the senators was the secrecy of the experiments, which involved a large population of involuntary and unwitting subjects. Senator Richard Schweiker chastised the United States Army for continuing the use of *S. marcescens* as a biologic marker despite the fact that as early as 1952, Army personnel had been aware of the Stanford outbreak; yet the organism continued to be used as a biologic marker until 1968. Under the administration of President Richard Nixon, biologic warfare was denounced by the United States in 1969, and production of such biologic agents was halted. Spokesmen for the Army were in the uncomfortable position of having to defend decisions made by others 20 to 30 years previously. Testimony from expert witnesses in the academic community not only questioned whether any microorganism could ever be considered wholly harmless but also criticized the scientific merits of the aerosolization experiments, citing design flaws and the limited usefulness of any information obtained.

Subsequent analysis has cast doubt on the part that these aerosolization experiments may have played in the causation of infections. The Center for Disease Control in Atlanta, Georgia, has reported that in 100 outbreaks caused by *S. marcescens* in the United States, none were caused by a strain of serrata with the same serotype and biotype as that used by the United States Army. Also, in retrospect, the cases described in Wheat’s report are strikingly similar to the serrata outbreaks of today—namely, nosocomial infections in catheterized, debilitated patients. Thus, Wheat’s report may have merely represented a portent for future nosocomial infections rather than a description of cases resulting from the United States Army’s aerosolization experiments.

**Association with Intravenous Drug Abuse**

In 1973, Fishbach et al. reported a case of vertebral osteomyelitis caused by *S. marcescens* in a heroin addict. This report was followed in succession by descriptions of endocarditis, septic arthritis and osteomyelitis caused by *S. marcescens*. These reports shared two features: virtually all the patients were heroin addicts, and all lived in California.

The Mills and Drew report is of particular interest: they noted 19 cases of serrata endocarditis in one San Francisco Bay Area hospital from 1963 to 1974. Before their report in 1976, only 12 cases of serrata endocarditis had been recorded in the English-language literature. In contrast to these previous 12 cases, almost all the cases in San Francisco were associated with intravenous drug abuse. In addition, the San Francisco cases were characterized by a high frequency of embolic complications and a refractoriness to medical therapy. Although the route of entry for the organism was presumably intravenous, environmental cultures and epidemiologic surveys failed to uncover the source. Mills and Drew suggested that one possible explanation was the use of *S. marcescens* in the United States Army germ-warfare studies conducted in San Francisco. In rebuttal, the Army noted that during the experiments conducted in 1952, the organisms were known to have decayed rapidly, and none remained after 24 hours. They considered it improbable that these organisms could persist from the 1950’s to 1963, when the first case of serrata endocarditis was detected. It has subsequently been determined that the serotype of the *S. marcescens* strain used for the aerosolization experiments is antigenically different from the multiple serotypes of *S. marcescens* isolated from the endocarditis patients (Mills J, personal communication). Thus, the reason for this geographic clustering of serrata endocarditis remains unknown.

**Cause of Nosocomial Infections**

The recent notoriety of *S. marcescens* is a result of its importance as a cause of serious nosocomial infection. Although early reports noted the pigmentation of the organism, nonpigmented strains have been implicated in nosocomial infections. Ewing et al. studied a large number of isolates from different hospitals and noted that certain serotypes predomin-
ated in a particular hospital over a given time, suggesting that these infections were a result of cross-infection among patients.24

The first description of nosocomial infection caused by *S. marcescens* was Wheat’s previously cited report of 11 cases in a six-month period in 1951 at Stanford University Hospital.21 In 1952, Rabinowitz and Schiffrin reported the first well documented outbreak attributable to point-source dissemination of *S. marcescens*.22 Eleven cases of meningitis, wound infection and arthritis occurred on a pediatric ward; the probable source of the organism was an intravenous solution contaminated with *S. marcescens*. In 1966, McCormack and Kunin described a nursery epidemic involving 27 babies. The source of this epidemic was traced to contamination of plastic caps of saline bottles from which fluid was used to moisten umbilical cords.23

Solutions contaminated with *S. marcescens* that have caused subsequent outbreaks have included disinfectants (hexachlorophene, benzalkonium chloride), water from ultrasonic nebulizers and intermittent positive-pressure machine reservoirs, intravenous solutions and even hand lotions.24-26 Since *S. marcescens* thrives in moist environments, including medicated solutions, there are situations in which rapid dispersal can easily occur. Medical equipment implicated in the dispersal of *S. marcescens* in hospital epidemics includes mechanical respirators, intermittent positive-pressure breathing machines, ultrasonic nebulizers, polyethylene intravenous catheters, scalp-vein needles, arterial-pressure monitors and fiberoptic bronchoscopes.27-30,33-35 Even contamination of the bristles in shaving brushes has been reported; outbreaks occurred in an intensive-care unit where such brushes were used for patient grooming.31 Procedures associated with iatrogenically induced *S. marcescens* infection include genitourinary manipulation, peritoneal dialysis and hemodialysis, blood transfusions, intravascular catheterization and lumbar puncture.31,32,34,37,80-82 The organism has been isolated from the floors of rooms occupied by infected or colonized patients and from dust particles within those rooms.83,84,85

The predominant mode of spread, however, appears to be hand-to-hand transmission by hospital personnel, with point-source outbreaks, as described above, accounting for a minority of cases. The importance of the urinary tract as a reservoir for colonization and the presence of an indwelling bladder catheter as a risk factor for *S. marcescens* infection deserve special emphasis. The risk of infection of a catheterized patient by *S. marcescens* varies with the proximity of that patient to other catheterized patients who already have colonies of the organism.36,37,86 The respiratory tract is an important portal of entry for patients who undergo manipulative airway procedures. In this group, differentiation between patients who are infected and those with colonies of *S. marcescens* can be a difficult clinical problem. The gastrointestinal tract is not an important reservoir in adults but may be a primary reservoir in children.35,36

The use of antimicrobial drugs is commonly accepted as a risk factor for the development of *S. marcescens* infections, although studies performed with adequate controls are not available. However, the use of antimicrobial drugs has been documented as a risk factor for the emergence of drug-resistant strains. For example, Yu et al. have demonstrated that not only the use of gentamicin itself but also the total dosage and duration of therapy are risk factors for the emergence of gentamicin-resistant strains.19 Other commonly reported associations include patient debility, compromised host status, surgery and corticosteroid therapy.10,35,37,36 It is not known whether these risk factors are truly independent or merely associated with prolonged hospitalization, broad-spectrum antimicrobial drug use and respiratory- and urinary-tract manipulation.

Hospital-infection surveillance has been important in combating *S. marcescens* infections, not only by identifying point sources of the organism but also in localizing reservoirs for the organism and allowing early implementation of infection-control measures. In outbreaks where no point source of *S. marcescens* can be found, infection-control measures have met with variable success.35,39,40 Although the frequency of *S. marcescens* infection may respond initially to strict infection-control measures, when such measures are relaxed, upswings in the rate of infection usually occur. Recommended measures include the washing of hands by hospital personnel, the removal of indwelling catheters, the use of aseptic techniques during manipulative procedures and the cohorting and isolation of colonized and infected patients.40,41 Judicious use of antimicrobial agents is routinely advocated but is rarely implemented on any formal basis.

The most dramatic outbreak of nosocomial *S. marcescens* infections occurred in Nashville, Tennessee, where an epidemic strain of *S. marcescens* resistant to all commercially available antibiotics infected patients at four geographically separate hospitals.41,42 Three of the hospitals were teaching hospitals of the Vanderbilt University School of Medicine, with physicians and nurses regularly rotating among all hospitals. In April, 1973, a drug-resistant strain was first isolated from the urine of a catheterized patient in one hospital. By late 1974, four hospitals in that area had outbreaks of infections with the same organism as defined by serotype, phage type and antimicrobial sensitivity pattern. In a 21-month period, 210 patients became infected, and 21 patients had become bacteremic. Interhospital transmission of *S. marcescens* probably occurred via passive carriage of the hands, since the epidemic strain could be isolated from pooled hand-rinseings of hospital personnel. Subsequently, one of the four hospitals experienced a second wave of infections caused by multiply drug-resistant klebsiella.41 In vitro mating studies revealed that the multiple drug resistance of the serrata strain
was transferable to the klebsiella strain via plasmids. Since both organisms were shown to have plasmids of equal molecular weight, the investigators speculated that the temporal sequence of klebsiella infections superseding the serraita infections may have been a result of an in vivo transfer of resistance plasmids.

As discussed, a major clinical concern about *S. marcescens* is its antibiotic resistance. Although early reports noted that the organism was usually susceptible to kanamycin and always susceptible to gentamicin in vitro, recent reports have demonstrated the existence of *S. marcescens* strains that are multiply drug resistant, including gentamicin. Resistance is generally plasmid-mediated. Medeiros and O'Brien found that plasmids not only mediated resistance to antimicrobials to which the strain had previously been susceptible but also conferred additional degrees of resistance to antimicrobial agents to which the organism was already resistant. The organism is invariably resistant to cephalothin, the tetracyclines and the penicillins, including carbencillin. Variable sensitivity in vitro exists for chloramphenicol, nalidixic acid, trimethoprim-sulfamethoxazole, cefoxitin, cephamandole and the aminoglycosides. When the organism is resistant to gentamicin in vitro, amikacin is usually the drug of choice. However, isolation of amikacin-resistant organisms is now being reported, and the resistance of such strains may become a problem in the future. Synergistic combinations of trimethoprim-sulfamethoxazole with colistin, rifampin with polymyxin, carbencillin with aminoglycosides and cefoxitin with aminoglycosides have been reported to be successful against various multi-drug resistant strains.

**Conclusions**

*Seratia marcescens* has in the past risen from a humble role as a mere saprophyte to that of a "miracle bacterium," evoking both marvel and consternation, so that it has become embedded in religious folklore and classical history. In the 20th century, the role of *S. marcescens* has been no less dramatic. As a biologic marker, it has had a leading role in a number of classic experiments, which led to an improved understanding of the pathogenesis of infection. As a result of its use in germ-warfare studies, it received headlines in the lay press. Now, it has graduated to the full-fledged status of a pathogen that causes difficult-to-treat infections in two disparate groups: heroin addicts and hospitalized patients.

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**References**

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