Lange, Charles Edward Ⓜ Chickasaw, Ala; *University of Texas*, 1942; died in Chickasaw Infirmary May 8, aged 47, of myocardial infarction and hypertensive cardiovascular disease.

Levey, Philip Ⓜ Los Angeles; *Creighton*, 1913; veteran of World War I; affiliated with Midway, Temple, Westside, Sunset, and San Vicente hospitals; died May 19, aged 76, of a heart attack.

Levin, Hyman Loeb Ⓜ Buffalo; *University of Buffalo*, 1911; certified by the American Board of Psychiatry and Neurology; served on the staff of the Buffalo State Hospital; on the faculty of his alma mater; died May 30, aged 80, of coronary thrombosis.

Levy, Saul Mortimer, Miami Beach, Fla; *Cornell*, 1910; died May 27, aged 79, of arteriosclerotic heart disease.

Marks, Walker Roscoe Ⓜ Vinita, Okla; *University of Illinois*, 1912; veteran of World War I; on the staff of the Craig General Hospital, where he died May 21, aged 75, of carcinoma of the throat.

McElvain, Robert Childers Ⓜ Boca Raton, Fla; *University of Illinois*, 1910; for many years practiced in St. Louis, where he was on the staff of the Christian Hospital; died in the North District Hospital in Pompano Beach May 29, aged 78, of arteriosclerotic heart disease.

McMahon, Henry Oliver Ⓜ Milwaukee; born in New Brighton, Pa, March 3, 1877; *Detroit Homeopathic College*, 1902; veteran of World War I; on the faculty of the Marquette University School of Medicine; member of the Wisconsin State Board of Medical Examiners; past president of the Milwaukee Pediatrics Society; health officer of River Hills, Wis; on the staff of St. Mary's Hospital; died in St. Michael Hospital May 31, aged 88, of ruptured arteriosclerotic aneurysm of the abdominal aorta.

Monfort, John Joel Ⓜ Batesville, Ark; *Oklahoma*, 1932; past president of the Arkansas Medical Society; veteran of World War II; affiliated with Dr. Gray's and North Arkansas Clinic hospitals; died May 24, aged 57, of coronary thrombosis.

Nordland, Martin Albert, Jr. Ⓜ Minneapolis; *Minnesota*, 1945; served as a fellow in surgery of the Mayo Graduate School of Medicine, University of Minnesota in Rochester; member of the surgical staff of the Northwestern Hospital; died May 30, aged 44, of coronary insufficiency.

O'Hanlon, John Anthony Ⓜ Minneapolis; *Marquette*, 1933; died May 14, aged 59, of coronary occlusion.

Osborn, Harold Blackman Ⓜ Fillmore, Calif; *South Carolina*, 1909; veteran of World War I; on the staff of the Ventura Community Memorial Hospital and the Santa Paula Memorial Hospital, where he died May 30, aged 81, of pneumonia

Patzer, Reynold Ⓜ Oklahoma City; *Loma Linda*, 1937; certified by the National Board of Medical Examiners; served on the faculty of the University of Oklahoma School of Medicine; died May 24, aged 58, of myocardial infarction.

Reed, Robert Barthold, Fairborn, Ohio; *Ohio State*, 1920; died in New Carlisle May 28, aged 68, of myocardial infarction and coronary arteriosclerosis.

Reynolds, David Duer Ⓜ Kennett Square, Pa; *University of Pennsylvania*, 1916; veteran of World War I; died in Wilmington, Del, May 31, aged 75, of prostatic cancer and uremia.

Rhodes, Roy McKinley Ⓜ New York; *Medical College of Virginia*, 1926; died in the House of Calvary Hospital May 31, aged 64.

Rittenberg, Leonard Milton, New York; *University and Bellevue Hospital Medical College, New York*, 1928; veteran of World War II; died in the Presbyterian Hospital May 30, aged 61, of cerebral hemorrhage.

Saunders, Cecil Allen, Jr. Ⓜ Honolulu, Hawaii; *University of Southern California*, 1952; certified by the National Board of Medical Examiners; died in the Queen's Hospital May 30, aged 45, of bilateral pneumonia.

Seabrooks, Benjamin Franklin, Jr. Ⓜ Detroit; *Meharry*, 1929; died in the Woodward General Hospital May 25, aged 62, of myocardial infarction and diabetes mellitus.

Sebastian, Stephen Edward Ⓜ Milwaukee; *Marquette*, 1923; veteran of World War I; associated with the US Veterans Administration; died May 23, aged 69, of coronary heart disease.

Stamm, Leander Peter Ⓜ Milwaukee; *Marquette*, 1916; veteran of World War I; served on the staff of St. Joseph's and St. Michael hospitals; died May 8, aged 71, of cancer of the prostate.

Strain, Samuel Frederick, Jr. Ⓜ Memphis; *University of Tennessee*, 1954; on the faculty of his alma mater; on the staff of the Baptist Hospital, where he died May 15, aged 38, of glioblastoma multiforme.

Tiers, Francis Merkling Ⓜ Jersey City, NJ; *Temple*, 1956; certified by the American Board of Anesthesiology; affiliated with the Jersey City Medical Center; found dead May 24, aged 38, of suicide by sodium pentothal.

Topham, Edward Ⓜ San Francisco; *University of California, San Francisco*, 1902; served on the faculty of his alma mater; for many years on the staff of St. Mary's Hospital; died in the Notre Dame Hospital May 21, aged 85, of arteriosclerosis.

Van Heuven, J. Alexander Ⓜ New Haven, Conn; *Rijks-Universiteit te Utrecht Faculteit der Geneeskunde, Netherlands*, 1923; certified by the American Board of Ophthalmology; on the faculty of Yale University School of Medicine; affiliated with the Grace-New Haven Hospital and the Hospital of St. Raphael, where he died May 26, aged 66, of myocardial infarction.

Ward, Emery Mittchell Ⓜ Boulder, Colo; *University of Virginia*, 1953; veteran of World War II; died May 21, aged 45, of accidental drowning.

Webb, Walter Whayne Ⓜ Dayton, Ohio; born in Jasper, Tenn, Aug 5, 1906; *Northwestern*, 1933; certified by the American Board of Otolaryngology; served on the faculty of his alma mater and the State University of Iowa College of Medicine in Iowa City; affiliated with Miami Valley and St. Elizabeth's hospitals; on the staff of the Kettering Hospital in Loudonville, where he died May 9, aged 58, of pulmonary hemorrhage due to lipoid pneumonia.

Published Under the Auspices of The Board of Trustees

THE JOURNAL of the American Medical Association

JAMA

VOL 193, NO 9, August 30, 1965

Control of a Staphylococcal Outbreak in a Nursery

Use of Bacterial Interference

Irwin J. Light, MD, James M. Sutherland, MD, and Jean E. Schott, MS

An outbreak of pathogenic staphylococci was recognized in a newborn and premature service. When conventional control measures failed, the phenomenon of bacterial interference was exploited. Deliberate colonization of infants was carried out with a relatively nonpathogenic, coagulase-positive, penicillin-sensitive *Staphylococcus* (502A). The procedure was carried out in a simple manner and was effective in controlling the outbreak. No major pyogenic lesions attributable to the 502A strain were noted in either the full-term or premature infants. Acquisition of the interfering strain by the infants was prevented if antibiotic drugs were administered or if staphylococci had already been acquired. The ability to isolate all coagulase-positive staphylococci, including 502A, from the umbilical site of premature infants decreased with increasing age of the patients.

Reawareness of bacterial interference challenges traditional concepts of human bacterial interaction in the pathogenesis of microbial disease. Interest in bacterial interference between strains of staphylococci was renewed when Shinefield et al[1] isolated from patients a coagulase-positive *Staphylococcus* which was associated with mild and infrequent disease. This strain of *Staphylococcus aureus* was designated 502A. Once established in an individual this organism prevents the later acquisition of other strains of staphylococci.[1-3]

For editorial comment, see page 735.

When an outbreak of pathogenic staphylococci was recognized in a nursery service, and when orthodox control measures failed, deliberate colonization with the 502A strain was employed in an effort to terminate the outbreak. The present paper describes the outbreak and its ultimate control by this means.

From the departments of pediatrics and obstetrics, University of Cincinnati, Cincinnati General Hospital, and the Children's Hospital Research Foundation, Cincinnati.

Read in part before the Midwest Society for Pediatric Research in Winnipeg, October 14, 1964.

Reprint requests to Elland Ave and Bethesda, Cincinnati 45229 (Dr. Light).

Material and Methods

Nursery Units.—The nurseries for full-term infants and the procedures used in the care of these infants have been described.[2-4] Infants weighing less than 2,200 gm (4.8 lb) at birth are housed in a separate unit in another building. Total floor space in this low-birth-weight unit is 1,200 sq ft. The unit consists of an admission room with 12 incubators, two graduation rooms—each with six bassinets—and an observation (isolation) unit with two bassinets. The average census in this unit is 20 infants and the capacity is 25 infants. Procedures are similar to those in the full-term nurseries.

The Outbreak in the Full-Term Nursery.—On one day each week bacteriological survey for staphylococci is carried out by culturing specimens from the noses of all infants being discharged that day and of all infants more than 7 days of age. In the full-term nursery no staphylococci of the bacteriophage type 80/81 were isolated in the 16 weeks immediately preceding Jan 1, 1964. Furthermore, staphylococci of bacteriophage type 80/81 were cultured from only six infants in the 80 weeks preceding this time. The organisms were cultured from single infants during the 17th, 23rd, and 27th week prior to Jan 1, 1964, and from three infants during the 24th week prior to this date.

During the period following Jan 1, 1964, staphylococci of the bacteriophage type 80/81 were isolated during 14 of 17 weeks. Organisms were isolated from one to five infants on these individual weekly surveys: 36 such infants were identified. Nineteen infants or mothers with severe pyogenic lesions were noted during this 17-week period: eight infants and eight mothers with breast abscesses, one infant with pyarthrosis of the hip, one infant with suppurative parotitis, and one infant with osteomyelitis of a rib. Many infants had pustular skin lesions during hospitalization or after hospital discharge.

Four unsuccessful attempts were made to control the outbreak. The nursery was closed to new admissions until infants had been discharged and the nursery emptied and cleaned. Meanwhile, new

infants were admitted to a nursery opened in another part of the department. Specimens from all personnel were cultured and all infants with suspicious pyogenic lesions were removed from the nursery.

The Outbreak in the Premature Nursery.—In the premature nursery no type 80/81 staphylococci were detected during a period of 21 weeks prior to Jan 1, 1964. Thereafter, five infants with positive nasal cultures were detected in a three-week period, though no significant pathogenic lesions were noted.

The Inoculum.—The organism employed for artificial colonization was a coagulase-positive, penicillin-sensitive, relatively nonpathogenic *Staphylococcus* designated 502A.

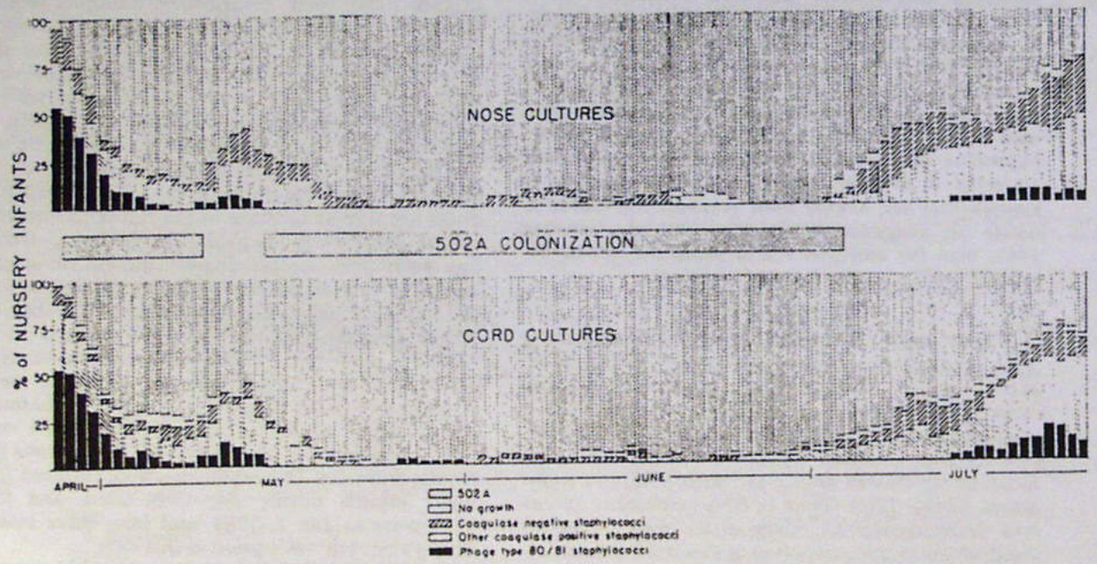
The coagulase-positive *Staphylococcus* designated 502A[1] is a nonpenicillinase-producing organism. This strain is extremely sensitive to penicillin G. As tested by disc sensitivity methods it is sensitive to 2 units of penicillin, 2μg of erythromycin, 2μg of oleandomycin, 5μg of kanamycin sulfate, 5μg of novobiocin, and 10μg of tetracycline, but it is resistant to 5μg of tetracycline. It is lysed by some of the group III bacteriophages, usually one or more of bacteriophages 7, 47, 53, 54, and 77. Serologically the organism has been designated (b) C_1 but the strong C_1 reaction is most useful in its typing.[1]

An inoculum in trypticase soy broth (BBL 01-162) was grown for 18 hours and then diluted with broth (BBL 01-162) so that 0.01 cc contained approximately 5,000 organisms (a 1:200 dilution of the 18-hour broth). The diluted broth culture was then divided into 1.0 cc aliquots in separate test-tubes and stored in the refrigerator. Broth cultures were prepared daily from a reference slant. The antibiotic disc sensitivity pattern was determined daily on the broth culture to assure identity of the inoculum.

Technique of Colonization.—Specimens from all infants in the premature nursery on the initial day of the study were cultured and then a single colonization was performed on each infant. All infants admitted to either the premature or to the full-term nursery after the beginning of the study were colonized within two hours of birth.

Initially colonization was carried out by utilizing an 0.25 cc syringe and administering a measured 0.01 cc to each of the external nares and to the base of the umbilicus. Colony counts on dilutions of the inoculum confirmed that the dose administered was 1,100 to 11,500 organisms. Having determined the safety and the efficiency of this procedure in 34 premature infants, the technique was modified to permit routine colonization of all infants by the nurse. A dry, sterile cotton swab was moistened in 1.0 cc of diluted broth culture and swept around the base of the umbilicus. Each of the external nares was colonized in a similar fashion with separate swabs. By weighing the swabs before and after implantation, an estimated 10,000 staphylococci (with a range of 2,000 to 50,000) were administered to each site. A separate tube of broth was used for each infant.

Bacteriological Methods.—Initially specimens from infants in the premature nursery were cultured immediately prior to colonization, 24 to 48 hours



1. Daily staphylococcal flora in full-term infants. Mean number of infants tabulated each day was 44 (range: 27-64).

Table 1.—Infants Colonized With 502A Strain

Sites of 502A Strain	Number	"Takes"* No.	"Takes"* %
Full-term infants			
Nose	470	446	95
Cord	470	443	94
Both sites	940	889	95
Premature infants			
Nose	114	84	74
Cord	112	77	69
Both sites	226	161	71
All sites	1,166	1,050	90

*Recovery of one or more colonies of 502A strain on cultures taken 24 hours or more after artificial colonization.

after colonization, and then at one-week intervals. Later, only weekly cultures were obtained, for virtually all cultures obtained on admission and prior to inoculation were negative for staphylococci. Specimens from full-term infants were cultured on the day of discharge from the hospital, usually at 4 to 5 days of age. From infants remaining in the nursery seven days or longer, cultures were obtained at weekly intervals. Umbilical cultures were obtained from the base of the umbilical cord or from the skin of the healed umbilical site. Nasal cultures were obtained by inserting a dry cotton swab into one nostril. Swabs streaked directly onto mannitol salt agar (BBL 01-319) were incubated for 48 hours, and examined for colonial morphology, pigmentation, and mannitol fermentation. All staphylococci were tested for coagulase production by a standard slide test with rabbit plasma (BBL 73-056). A test-tube coagulase determination was performed if the result of the slide test was equivocal or if the slide test did not parallel mannitol fermentation. Antibiotic disc sensitivity patterns were performed on all mannitol-positive coagulase-positive strains of staphylococci (*S aureus*) using the following discs: penicillin, 2 units; tetracycline, 5μg and 10μg; erythromycin, 2μg; oleandomycin, 2μg; kanamycin, 5μg; novobiocin, 5μg. The 502A strain was consistently sensitive to all discs but the 5μg tetracycline disc. In the latter part of the study bacteriophage typing was limited to coagulase-positive staphylococci not demonstrating the typical 502A sensitivity pattern.

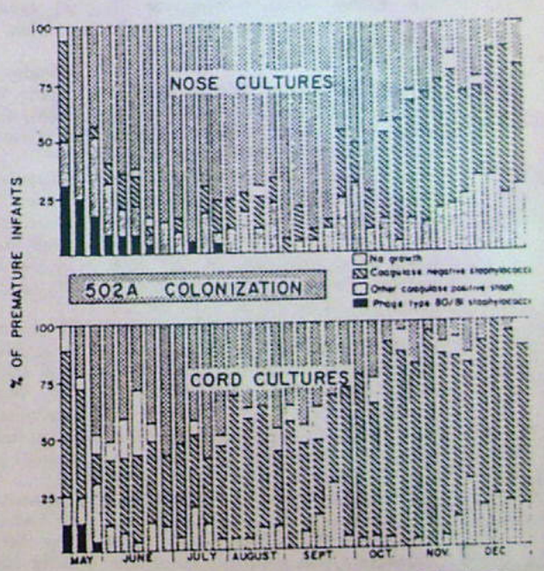
Results

Full-Term Nursery.—A total of 940 cultures were obtained from 470 artificially colonized full-term infants (Table 1). A "take" was defined as the recovery of one or more colonies of 502A strain on cultures taken 24 hours or more after colonization.

There were 95% successful "takes" in the nose and 94% successful "takes" at the umbilical site.

A daily epidemiologic survey of all infants in the nursery was compiled from available data (Fig 1). (If infants were discharged before one week of age it was assumed that the infant harbored from birth the organism which was isolated at discharge. If infants remained in the nursery after one week of age, it was assumed that the organisms isolated from the weekly or the discharge culture had been present throughout the interval since the preceding culture.) Following the onset of artificial colonization the 502A organism displaced from the nursery all other coagulase-positive staphylococci including those of bacteriophage type 80/81 from both the nose and cord. The 80/81 organism reappeared when colonization was discontinued. Artificial colonization was reinstituted and the 502A strain again became the dominant *Staphylococcus*, displacing all other coagulase-positive staphylococci from the nursery. Colonization was discontinued after seven consecutive weeks. Thereafter, other coagulase-positive organisms reappeared as the 502A strain slowly disappeared. The 502A organism isolated in the postcolonization period were from both artificially and spontaneously colonized infants. Infants who had been purposefully implanted with the 502A strain were still in the nursery. Two hundred and thirty-six full-term infants were admitted to the nursery in the 21 days after artificial colonization had been discontinued. Of these infants 159 (67%) spontaneously acquired the 502A organism.

Premature Nursery.—A total of 226 specimens for culture were obtained from 114 premature infants at intervals of one to seven days after colonization (Table 1). There were 74% successful "takes" in the nose and 69% at the umbilical site. The results of cultures are graphically represented on a weekly basis (Fig 2). In the nose, coagulase-positive staphylococci including bacteriophage type 80/81 were displaced by the 502A strain, though other coagulase-positive staphylococci persisted in 5% to 20% of infants. Following cessation of artificial colonization 502A slowly disappeared from the nursery. Only 50% to 60% of the infants car-



2. Weekly staphylococcal flora in premature infants. On given day each week cultures were obtained from all infants. Mean number of infants cultured each week was 21 (range: 16-25).

Table 2.—Effect of Previous Flora on 31 Premature Infants Not Receiving Antibiotics*

Flora Prior To Colonization	"Takes" Nose	Cord	Both	
S aureus†	2/10	0/6	2/16	12%
Other staphylococci‡	9/11	1/7	10/18	55%
No staphylococci§	9/9	8/12	17/21	81%

*Cultured immediately before and 24 to 48 hours after colonization.
†Mannitol-positive, coagulase-positive staphylococci are designated "*S aureus*."
‡"Other staphylococci" are staphylococci which are not both mannitol-positive and coagulase-positive.
§"No staphylococci" indicate that staphylococci could not be isolated, though in a few instances other organisms were found.

ried the 502A strain at the umbilical site at any one time. Of those who did not have 502A at the umbilical site, few had coagulase-positive staphylococci and many had coagulase-negative staphylococci.

Effect of Previous Flora.—In 31 premature infants ranging in age from 6 days to 6 weeks, and not receiving antibiotics, a total of 55 sites were cultured immediately before and 24 to 48 hours after artificial colonization (Table 2). At those sites with preexisting mannitol-positive and coagulase-positive organisms (*S aureus*) there were only 12% "takes." At sites with staphylococci which were not both mannitol-positive and coagulase-positive, 55% "takes" occurred. At those sites not already spontaneously colonized with staphylococci there were 81% of successful "takes." In the nose, there are significant differences between those with preexisting *S aureus* and those with either no staphylococci (chi-square, with Yates correction, one degree of freedom, is 6.30, $P < 0.02$) or with staphylococci other than *S aureus* (chi-square, with Yates correction, one degree of freedom, is 5.64, $P < 0.02$). No significant difference could be demonstrated between those with staphylococci other than *S aureus* and those with no staphylococci (chi-square, one degree of freedom, is 0.36, $P > 0.50$).

At the umbilical site the figures obtained are too small for meaningful statistical analysis. However, the difference between those with preexisting *S aureus* and those with no staphylococci is significant (chi-square, with Yates correction, one degree of freedom is 4.75, $P < 0.05$).

Effect of Antibiotics.—Of the 114 premature infants studied, 36 infants were receiving antibiotics at the time they were colonized or prior to the first follow-up culture (Table 3). The 502A strain was recovered from 47% of 70 sites cultured 24 hours or more after colonization. The difference in "takes" at sites in premature infants receiving antibiotics is significantly different from "takes" at both nose (chi-square, with Yates correction, one degree of freedom, is 10.34, $P < 0.01$) and umbilical sites (chi-square, with Yates correction, one degree of freedom, is 15.48, $P < 0.01$) in infants not receiving drugs.

One hundred and forty-three sites were cultured in 72 premature infants not receiving antibiotics and without staphylococci before artificial colonization (Table 4). In this group 92% successful "takes" were obtained. This is similar to the 95% successful "takes" in 447 full-term infants who were colonized within two hours of age and who did not receive antibiotics (Table 1).

Effect of Age.—Premature infants remained in the nursery for as long as 12 weeks. In the first week (Fig 3) 85% of premature infants had acquired coagulase-positive staphylococci artificially or spontaneously in the nose. This rate showed little change in infants who were followed for as long as 12 weeks. At the umbilical site 85% of premature infants acquired coagulase-positive staphylococci by the time they were 1 week of age. The percentage of infants from whom coagulase-positive organisms were isolated from the cord (502A or other strains) decreased to 5% by 7 to 12 weeks. At the same time, the proportion of infants from whom coagulase-positive organisms were isolated at the cord cite increased to 80% at 7 to 12 weeks.

Comment

A system of bacterial surveillance permitted early recognition of a nursery outbreak of *S aureus* of the bacteriophage type 80/81. Severe pyogenic lesions in infants and mothers demonstrated the pathogenicity of this strain. Conventional methods of control proved of little value. Therefore, bacterial interference was utilized to control the outbreak: all infants were artificially colonized within 2 hours of age with a nonpathogenic, coagulase-positive *S aureus* (502A).

The procedure was effective. During the two inoculation periods the 502A strain displaced from the nursery other coagulase-positive staphylococci including those bacteriophage type 80/81. After both periods, other coagulase-positive staphylococci returned. The simple technique of colonization was performed by nurses as part of the routine nursery admission.

The 502A strain was administered safely to full-term and premature infants. No major pyogenic lesions attributable to the 502A strain were noted. In rare instances (less than 5%) tiny vesiculopustular skin lesions occurred and the 502A organism was isolated. The safety of this strain was well documented in full-term infants by Shinefield and coworkers.[3] They found five instances of minor local disease among 524 infants who had been inoculated with 502A. They found a much higher incidence of lesions in infants under study who were not inoculated with 502A and who spontaneously acquired bacteriophage type 80/81 staphylococci.

Table 3.—Effect of Antibiotics*

Site of Culture	Number of Infants Receiving Antibiotics	"Takes" No.	%
Nose	36	19	53
Cord	34	14	41
Both sites	70	33	47

*Of total 114 premature infants studied, 36 infants received antibiotics on day of colonization or prior to first follow-up culture.

The present study demonstrated the lack of pathogenicity of the 502A strain in premature infants as well as in full-term infants. In addition, in the present study a larger number of 502A staphylococci were used for colonization than had been used in previous infant studies.

Despite inadequate understanding of the phenomenon of bacterial interference several factors were shown to influence the colonization of newborn infants with staphylococci.

Preexisting Flora.—Preexisting staphylococci prevent the subsequent acquisition of other strains of coagulase-positive staphylococci. In the present study infants already colonized with *S aureus* did not easily "take" or acquire the 502A *Staphylococcus*. This finding is similar to the observations of Shinefield and associates.[1] When these workers first isolated the 502A strain, they noted that infants who spontaneously acquired this organism did not later acquire another *Staphylococcus*. In their first inoculation studies they found that infants already colonized with *S aureus* would not accept the 502A inoculum. Similar findings[4] were made in adult subjects and were extended by challenging the 502A carriers with bacteriophage type 80/81 organisms. The infant is an ideal candidate for artificial colonization since he may be considered bacteriologically sterile at birth. This is in contrast to the adult subject where pretreatment with antimicrobial agents may be necessary before obtaining a successful inoculation.[4]

Antimicrobial Drugs.—The acquisition of staphylococci is influenced by antibiotic drugs. Among hospitalized adults the acquisition of drug-resistant staphylococci increased among patients receiving antimicrobial therapy.[5] In the present study antibiotics were frequently, though not routinely, administered to premature infants. By administering these drugs and thereby eliminating the drug-sensitive nonpathogenic strains, and interfering with interspecies relationships, spontaneous colonization with drug-resistant organisms became possible.

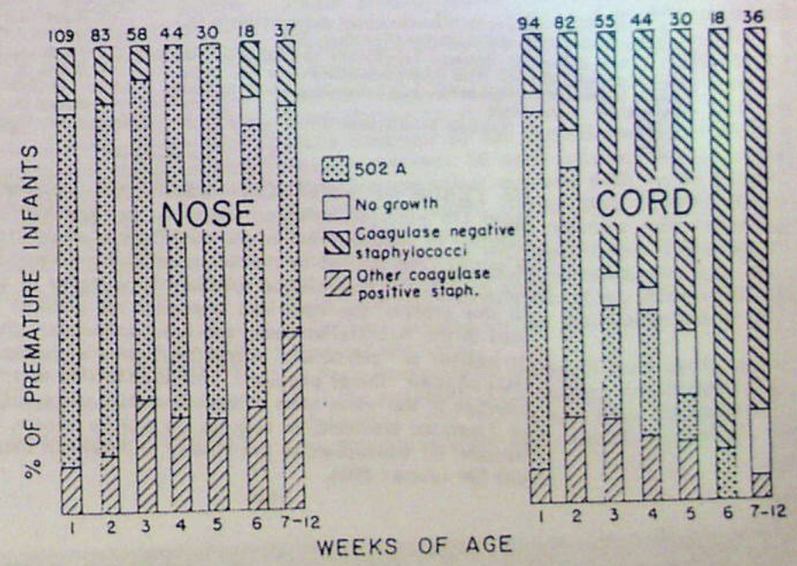
Table 4.—"Takes" in Premature Infants Not Receiving Antibiotics and Without Staphylococci Before Artificial Colonization

Site of Culture	Number	"Takes" No.	%
Nose	72	67	93
Cord	71	65	92
Both sites	143	132	92*

*92% of "takes" is similar to 95% of "takes" achieved in full-term infants colonized within two hours of age (Table 1).

Site and Age Differences.—Persistence of all coagulase-positive staphylococci, including those of the 502A strain, differs in the nose and at the umbilical site. In the nose the incidence of coagulase-positive staphylococcal carriers remains constant from 1 to 12 weeks of age. On the umbilical stump a similar incidence of coagulase-positive staphylococcal carriers is initially observed. Thereafter, the coagulase-positive staphylococci steadily disappear from the umbilical site and are replaced by coagulase-negative organisms. This shows that changes occur at the umbilical site with aging and the changes are detrimental to the survival of coagulase-positive staphylococci. Perhaps these organisms require the warm, moist mucous membranes of the nose or fresh umbilical stump for survival. Then as the cord becomes mummified and as the umbilicus heals, the coagulase-positive staphylococci are replaced.

Therefore, most of the differences noted in the present study between full-term and premature in-



3. Effect of age of premature infants on staphylococcal flora at nasal and umbilical sites. Number of infants in each age group is given above age bar.

fants resulted from differences in preexisting bacterial flora, administration of antibiotics, and the age of the patients. In the present study manipulation of bacterial flora with exploitation of the phenomenon of bacterial interference resulted in control of the staphylococcal outbreak.

Bacterial interference has been indirectly recognized for some time. The clinician is aware that long-term oral antibiotic therapy suppresses some gastrointestinal organisms and permits overgrowth of other organisms. Virologists recognize interference and have attributed it to a substance elaborated by viruses termed interferon. Microbiologists use in vitro selective media which inhibit some organisms and allow others to flourish and in vivo have shown that animals carrying *Escherichia coli* do not readily become superinfected with other strains of this bacterial species.[10]

This extracorporeal type of resistance is dependent on the fact that living bacterial agents in tissue interfere with colonization by other strains of the same species. The first organism of a species to become established at a site may in some manner, perhaps merely by numbers, be at an advantage in competing for available nutrients.[11] Or the initial organism may prevent colonization with other organisms of the same species by the elaboration of some as yet unidentified substance.[12,13] Such antibiotic substances, designated colicins,[14] are produced by certain strains of intestinal bacteria and inhibit growth of other related strains. Though explanation in this field of human bacterial ecology is only conjectural,[15,16] it has been demonstrated that the phenomena of bacterial interference may be effectively and safely employed to control a nursery outbreak of pathogenic staphylococci. In the face of an outbreak of these organisms the minimal risk associated with willful colonization with a relatively nonpathogenic organism appears justified. The routine purposeful colonization of all newborn infants in nonepidemic periods is not now recommended. However, evidence may be interpreted to suggest that controlled colonization of infants may be more desirable than the usual uncontrolled acquisition of organisms of variable pathogenicity. It is conceivable that at some future time traditional nursery asepsis and isolation will give way to controlled administration of safe and protective bacterial flora.

Technical assistance was rendered by Laurine Cochran, RN, Lois Adams, and Ruth Hotz, K.I.E. Macleod, MD, and T.A. Cockburn, MD, both with the Cincinnati Department of Health, provided some of the bacteriophage typing.

This investigation was supported by Public Health Service research grant HD 00578.

References

1. Shinefield, H.R., et al: Bacterial Interference. Its Effect on Nursery-Acquired Infection With *Staphylococcus aureus*: I. Preliminary Observations on Artificial Colonization of Newborns. *Amer J Dis Child* 105:646-654 (June) 1963.

2. Shinefield, H.R., et al: Bacterial Interference. Its Effect on Nursery-Acquired Infection With *Staphylococcus aureus*: II. Ohio Epidemic. *Amer J Dis Child* 105:655-662 (June) 1963.

3. Shinefield, H.R., et al: Bacterial Interference: Its Effect on Nursery-Acquired Infection With *Staphylococcus aureus*: III. Georgia Epidemic. *Amer J Dis Child* 105:663-673 (June) 1963.

4. Boris, M., et al: Bacterial Interference: Its Effects on Nursery-Acquired Infection With *Staphylococcus aureus*: IV. Louisiana Epidemic. *Amer J Dis Child* 105:674-682 (June) 1963.

5. Shinefield, H.R., et al: Bacterial Interference: Its Effect on Nursery-Acquired Infection With *Staphylococcus aureus*: V. Analysis and Interpretation. *Amer J Dis Child* 105:683-688 (June) 1963.

6. Sutherland, J.M., et al: Environmental Antimicrobiosis in a Nursery. *Amer J Dis Child* 102:793-806 (Dec) 1961.

7. Cohen, J.O., et al: Bacterial Interference: Its Effect on Nursery-Acquired Infection With *Staphylococcus aureus*: VI. Detection of Implanted *Staphylococcus aureus* Strain. *Amer J Dis Child* 105:689-691 (June) 1963.

8. Boris, M., et al: Bacterial Interference: Protection of Adults Against Nasal *Staphylococcus aureus* Infection After Colonization With a Heterologous *S aureus* Strain. *Amer J Dis Child* 108:252-261 (Sept) 1964.

9. Berntsen, C.A., and McDermott, W.: Increased Transmissibility of Staphylococci to Patients Receiving an Antimicrobial Drug. *New Eng J Med* 262:637-642 (March 31) 1960.

10. Sears, H.J., et al: Persistence of Individual Strains of Escherichia coli in Man and Dog Under Varying Conditions. *J Bact* 71:370-372 (March) 1956.

11. Ribble, J.C., and Shinefield, H.R.: Bacterial Interference in Experimental Staphylococcal Infections, read before the American Pediatric Society, Seattle, June 16-18, 1964, abstracted. *J Pediat* 65:1047-1049 (Dec, pt II) 1964.

12. Anthony, B.F., and Wannamaker, L.W.: Studies of Mechanisms of Bacterial Interference in Experimental Burns, read before the Society of Pediatric Research, Seattle, June 18-20, 1964, abstracted. *J Pediat* 65:1103 (Dec, pt II) 1964.

13. Resistance to Infection With *Staphylococcus aureus*, editorial. *JAMA* 190:391-392 (Oct 26) 1964.

14. Fredericq, P.: Colicins. *Ann Rev Microbiol* 11:7-22, 1957.

15. Dubos, R.: Staphylococci and Infection Immunity, editorial. *JAMA* 184:1038-1039 (June 29) 1963.

16. Dubos, R.: Staphylococci and Infection Immunity, editorial. *Amer J Dis Child* 105:643-645 (June) 1963.

175 YEARS OF AMERICAN MEDICINE.—Looking back over the span of about 175 years of American medicine, from the freedom gained under the Declaration of Independence to the contributions encompassed today in the totality of services represented by the American Medical Association, one must recognize the debt to the past and be mindful of the legacy of the present to the future. In this process, the American physician has justified the term "physician" as used in the Aristotelian sense and has, furthermore, given substance to the root derivatives of "physician," namely: *physikos* (scientist); *physiologus* (naturalist); *physika* (things physical), and *physike* (the art). If we wrap these aspects together in the warm balm of man's intellect and spirit, then the future advance of American medicine, in both its art and its science, is assured for all time.—Spector, B: Guideposts in the History of American Medicine, *Int Med Rec* 171: 323-330 (June) 1958.

In Vitro Susceptibility of Shigellae to Sodium Sulfadiazine and to Eight Antibiotics

Kenneth C. Haltalin, MD, and John D. Nelson, MD

More than 300 recently isolated *Shigella* strains were tested for susceptibility, to sodium sulfadiazine by tube and plate dilution techniques. With a low inoculum (100 organisms), 59% of *Shigella flexneri* and 87% of *S sonnei* were sulfadiazine resistant. All strains were resistant by high inoculum testing (2×10^8 organisms).

Antibiotic susceptibility testing by the plate dilution method using high inocula demonstrated by the following percentages of resistance: potassium penicillin G, 93%; streptomycin, 17%; tetracycline hydrochloride, 12%; chloramphenicol, 11%; ampicillin, 6%; sodium colistimethate, 2%; kanamycin sulfate, 1%; and neomycin sulfate, 1%. These studies indicate that sulfadiazine is no longer an appropriate drug for initiating treatment of shigellosis. Ampicillin and three orally administered nonabsorbable antibiotics (colistimethate, kanamycin and neomycin) are the most effective drugs against shigellae in vitro.

Sulfadiazine has been the most widely used drug for the treatment of shigellosis since Hardy and co-workers established its effectiveness two decades ago.[1-3]

At the present time several standard medical textbooks recommend sulfadiazine for the treatment of shigellosis[4-6] while others favor a broad spectrum antibiotic such as tetracycline.[8-10] The clinical importance of sulfadiazine-resistant shigellae is recognized by some[4,7,9] and not mentioned by others.[6,10] One textbook states that the reported high incidence of sulfadiazine resistance is more apparent than real and is due to the unreliability of sulfadiazine susceptibility tests as performed in most hospital laboratories.[7]

Because of the paucity of recent critical susceptibility data on which to base antimicrobial therapy, in vitro studies were undertaken to discover current sulfadiazine susceptibility patterns and to determine the efficacy of antibiotics. More than 300 recently isolated *Shigella* strains were tested against sulfadiazine and eight antibiotics—ampicillin (Polycillin), chloramphenicol (Chloromycetin), sodium colistimethate (Coly-Mycin Injectable), kanamycin sulfate (Kantrex), neomycin (Mycifradin) sulfate, potassium penicillin G, streptomycin sulfate, and tetracycline hydrochloride (Achromycin).

Read in part before the annual meeting of the Southern Society for Pediatric Research, Houston, Dec 5, 1964.

From the Department of Pediatrics, University of Texas Southwestern Medical School, Dallas.

Reprint requests to 5323 Harry Hines Blvd, Dallas 75235 (Dr. Haltalin).

Materials and Methods

Identification of Cultures.—Three hundred and forty recently isolated *Shigella* strains obtained from patients with acute diarrhea were studied. Two hundred and twenty-two were isolated in Dallas during the seven-month period from July 1963 through Jan 1964. Seventy additional strains had been obtained during a previous 2½-year period (January 1961 through June 1963).

All cultures were examined in this laboratory to ensure their purity and to confirm their identification. All strains acidified 1% glucose without the production of gas and did not blacken triple sugar iron agar. Urease was not produced and growth did not occur on Simmons citrate medium. Tests for the decarboxylation of lysine and the production of phenylpyruvic acid were negative. All strains were nonmotile. Serologic grouping was performed by the slide agglutination method using *Shigella* polyvalent antisera.

S flexneri strains comprised 78% of the cultures; *S sonnei*, 19%; *S boydii*, 2%; and *S dysenteriae*, 1%.

Cultures were maintained in paraffin-sealed nutrient agar stabs at room temperature.

Media.—The following media were used: Mueller-Hinton agar and Mueller-Hinton broth, 1% tryptone water, oxoid sensitivity test agar, and oxoid sensitivity test broth.

Sulfadiazine Testing.—Aqueous injectable sodium sulfadiazine was used. According to the manufacturer, the concentration of 250 mg/ml is accurate. (Personal communication from A. E. Tiesler.) This preparation is stabilized with 0.1% sodium sulfite which does not affect growth of shigellae.

Serial twofold dilutions of sulfadiazine were prepared aseptically in sterile phosphate-buffered normal saline (pH 7.2 to 7.4). Dilutions were freshly prepared for each batch of media. Frozen dilutions were unsatisfactory because precipitation occurred on thawing.

Plate Dilution Method.—One milliliter of a given