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BACTERIAL INTERFERENCE BETWEEN STRAINS OF *S. aureus*

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The ability of one strain of *S. aureus* to interfere with the growth of a second strain of *S. aureus* has been observed *in vitro* and *in vivo*, in animals and man. The phenomenon termed bacterial interference can be demonstrated in the test tube,[1, 2] the yolk sac of fertile hen's eggs,[3–7] burned surfaces of rabbits[8] and guinea pigs,[9] the nasal mucosa of guinea pigs,[10] and most recently on the nasal mucosa and intestinal tract of mice.[11, 12]

We have been interested in the phenomenon of bacterial interference in man for the past 10 years, and have particularly emphasized the use of the concept in clinical situations. In 1961, epidemiologic observations during a nursery outbreak of staphylococcal disease suggested to us that colonization of the nasal mucosa or umbilical stump of an infant by *S. aureus* prevented subsequent colonization at the same site by a second strain of *S. aureus*.[13]

In order to test this hypothesis, further observations by direct inoculation of *S. aureus* were made on a series of infants, medical students, nurses, and prisoner volunteers.[14, 15] For inoculation, a coagulase-positive *S. aureus* strain of low virulence was used, susceptible to penicillin and incapable of being induced to produce β-lactamase. The organism is lysed by group III staphylococcal phages and is referred to as strain 502A.

TABLE 1 presents the data on a series of 78 babies, deliberately colonized. A striking relationship was noted between the prior presence of *S. aureus* and the failure to implant strain 502A. Coagulase-negative staphylococci exerted a much weaker effect while under the conditions of the experiment. No interference could be demonstrated by other organisms that colonized the nasal mucosa.[13]

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	Number of Infants	Organis Staph Present
Take	68	38
No take	10	7
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* From Shinefield *et al.*[16] Ino was indicated by the presence o

Observations on adults o and studies. The human volu noncarriers of *S. aureus*, son with antimicrobials and the 502A or a second strain, ph ments were also performed. observed for 10 weeks after group of volunteers is prese that in adults as well as infan lococci interferes with subse positive staphylococci. The whether the individuals wer Persistence of the inoculated

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Carriers:	
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Noncarriers:	
treated with sodium oxacillin challenged with *S. aureus* 5(	
treated with placebo and cha with *S. aureus* 502A	

* From Shinefield *et al.*[16]

TABLE 1

TYPES OF ORGANISMS PRESENT ON NASAL MUCOSA RELATED TO SUCCESSFUL TAKES IN INFANTS OVER 24 HOURS OLD *

	Number of Infants	Organisms other than Staphylococcus		Staphylococcus Coagulase-negative		Staphylococcus Coagulase-positive	
		Present	Absent	Present	Absent	Present	Absent
Take	68	38	30	28	40	0	68
No take	10	7	3	8	2	4	6
		$\chi^2=0.31$; $p=0.62$		$\chi^2=4.04$; $p=0.05$		$\chi^2=13.88$; $p=0.001$	

* From Shinefield *et al.*[16] Inocula were of 500 or more bacteria. A successful take was indicated by the presence of marker 502A strain 24 hours after inoculation.

Observations on adults offered an opportunity for additional manipulation and studies. The human volunteer experiments involved persistent carriers and noncarriers of *S. aureus*, some of whom were treated locally and systemically with antimicrobials and then were challenged with either marker strains of 502A or a second strain, phage type 52/52A/80/81. Cross-challenge experiments were also performed. The patients and volunteers involved were usually observed for 10 weeks after the challenge; the summary of the data on one group of volunteers is presented in TABLE 2. The data offer direct evidence that in adults as well as infants, nasal colonization by coagulase-positive staphylococci interferes with subsequent colonization by other strains of coagulase-positive staphylococci. The ability to colonize noncarriers was independent of whether the individuals were treated with antimicrobials prior to challenge. Persistence of the inoculated strain, however, was significantly higher in non-

TABLE 2

COMPARISON OF TAKE AND PERSISTENCE RATES IN PERSISTENT NASAL CARRIERS AND PERSISTENT NASAL NONCARRIERS *

Subjects	Take		Persistence 3 weeks		Persistence 13–14 weeks	
	rate	%	rate	%	rate	%
Carriers:						
treated with sodium oxacillin and challenged with *S. aureus* 502A	13/13	100	11/13	85	7/13	54
treated with placebo and challenged with *S. aureus* 502A	9/14	64	3/9	33	1/9	11
Noncarriers:						
treated with sodium oxacillin and challenged with *S. aureus* 502A	15/18	83	11/15	73	7/15	47
treated with placebo and challenged with *S. aureus* 502A	17/18	94	7/17	41	5/17	29

* From Shinefield *et al.*[16]

TABLE 3

SITES OF SUCCESSFUL TAKES IN 8 CARRIERS TREATED WITH OXACILLIN AND INOCULATED WITH *S. aureus* 502A *

	Nose		Throat	
	Resident Strain	502A	Resident Strain	502A
Before therapy	8	—	8	—
After therapy	0	—	5	—
One month after inoculation with 502A	0	8	6	1

* From Shinefield *et al.*[16]

carriers who received antimicrobials than in subjects who did not receive antibiotics before inoculation.[14]

Other observations demonstrated that interference between strains of *S. aureus* was site-specific (TABLE 3). It can be seen that a resident strain on the nasal mucosa could be eliminated by intensive antimicrobial therapy. One month after inoculation with 502A, persistence of strain 502A at that site was noted. Antimicrobial therapy did not influence carriage of resident staphylococci on the oropharynx, however. Throat carriage of resident *S. aureus* was not influenced by nasal inoculation of 502A.[16]

Recently we have made a number of observations on prisoner volunteers, to determine specific factors involved in the take and persistence of inoculated *S. aureus*.[17] Experimental design differed from that of our previous studies. Larger numbers of microorganisms were used and the aerobic nasal flora were quantitated. In addition to local and systemic antibiotics, individuals were treated with germicidal soaps for one week prior to inoculation, and the inoculated sites included not only the nasal mucosa, but also the axillae, groin, and inguinal area. The data demonstrated that complete clearance of resident *S. aureus* from the nasal mucosa was an important factor in the take and persistence of the marker strain. TABLE 4 shows the data collected on 17

TABLE 4

COMPARISON OF STRAIN 502A PERSISTENCE IN GROUPS THAT LOSE OR RETAIN *S. aureus* AFTER SODIUM DICLOXACILLIN AND NEOSPORIN TREATMENT *

Subjects	Persistence of Strain 502A		
	7 days	13 weeks	23 weeks
Resident strain(s) of *S. aureus* eliminated after antibiotic treatment	17/17 (100%)	15/17 (88%)	8/11 (73%)
Resident strain(s) of *S. aureus* not eliminated after antibiotic treatment	8/11 (80%) (p=0.09)	2/10 (20%) (p=0.004)	1/6 (17%) (p=0.027)

* From Boris *et al.*[11]

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individuals in whom the *S. aureus* was completely eradicated prior to inoculation, as compared to 10 individuals in whom *S. aureus* persisted. Most striking were the differences in persistence rates at 23 weeks. In the group in whom the *S. aureus* resident strain was eliminated, the persistence rate was 73% (15 out of 17), whereas in the group who retained the resident *S. aureus* strain on the nasal mucosa the persistence rate was 17% (1 out of 6), a significant difference ($p = 0.027$).

Data obtained on an additional group of untreated carriers in this series of observations demonstrated that it was possible to overwhelm the nasal mucosa at least transiently with a large number of organisms. When doses in the range of 2.1×10^9 were used, it was possible to produce transient takes in all four individuals who were inoculated. Persistence was noted in only one at 70 days. In eight individuals inoculated with about 2.1×10^7 or 1.1×10^5 organisms, on the other hand, the take rate was only 50% and no persistence was noted in the eight individuals after 3 days. After a period of weeks, the persistent carriers were treated with an antimicrobial and with antigermicidals, and then were challenged with marker strain 502A. These individuals were similar to the other volunteer carriers in the study in that antimicrobial treatment with subsequent elimination of the resident strain of *S. aureus* rendered their nasal mucosa susceptible to colonization by a marker strain.

Additional crossover experiments demonstrated that the ability to interfere with colonization was not the property of a single strain, and the nasal mucosa that had been resistant to superinfection with the second strain could easily be colonized by a second strain if the interfering strain was removed with antimicrobial.

In summary, the data from observations on direct colonization by marker strains demonstrate that heavy colonization of the nasal mucosa of adults with *S. aureus* interfered with subsequent colonization by other *S. aureus* strains. The capacity to interfere was not restricted to a single *S. aureus* type. In addition, interference between strains of *S. aureus* was site-specific. The resistance to colonization by a second *S. aureus* strain appears to depend partly on the local presence of large numbers of resident staphylococci, since removal or suppression of this original strain renders the nasal mucosa increasingly susceptible to artificial colonization. The data collected also suggest that other factors besides the mere physical presence of staphylococci interfere with attempts to colonize the nasal mucosa. The unknown protective factors can be suppressed by antimicrobial therapy, or can be overwhelmed by repeated administration of large doses of *S. aureus*.

Application of the phenomenon of bacterial interference, in which staphylococci in humans were utilized in therapy, was first described by the Danish physician Schiotz in 1909. He noted that a patient with a staphylococcal throat infection, wrongly diagnosed as diphtheria, who was placed in the diphtheria ward did not become ill with disease. He than deliberately sprayed suspensions of staphylococci into the throats of the diphtheria carriers, and claimed good results in eliminating the carrier state.

We first used the phenomenon of interference in controlling severe outbreaks of staphylococcal disease in nurseries.[18–21] Several nurseries that cared for different population groups and engaged in a variety of nursery practices were studied. They had in common high infant colonization and disease rates due to a single strain of staphylococcus. Initially, half of the infants in the nurseries were artificially colonized with strain 502A on the nasal mucosa and

umbilical stump in the first few hours of life, while the other infants received placebo that consisted of saline solution. Hospital personnel who carried epidemic strains were permitted to continue their work, and the infants were followed at home for a period of a year, to determine their nasal colonization status and disease rates. It was conclusively demonstrated that nasal colonization with 502A afforded newborn infants virtually complete protection. Over the past seven years, at least eight nursery staphylococcal epidemics in which colonization with *S. aureus* 502A was used as a control measure have been reported. In no instance has this technique failed to curtail the epidemic.[18–23]

More than 4,000 infants have been colonized; from 5 to 15% of the infants colonized with 502A developed tiny vesicles around the umbilical area in the first few days of life. These spontaneously disappeared and were not a cause of concern. In one nursery, in a group of 50 infants, the rate of periumbilical lesions was reported to be 34%.[24] These infants were carefully followed up during a period of more than one year, and none of them developed any serious disease. Conjunctivitis associated with *S. aureus* 502A has also been seen in the newborn. There has been a single case of severe infection after colonization of an infant with *S. aureus* 502A.[25] This was an immature infant of a diabetic mother, who had been colonized at 3 hours of age. At 8 hours of age the infant was noted to be apneic, sluggish, and hypoglycemic. Through this colonized umbilical site, a polyethylene catheter was inserted into the umbilical vein and infusion was begun with 15% glucose. Treatment was delayed until the infant was 68 hours old. He died at 84 hours of age of septicemia and meningitis. Cultures from the blood and peritoneum grew both *S. aureus* 502A and *E. coli*. Post mortem cultures of the meninges grew *S. aureus* 502A. It should be noted that the one serious complication in 4,000 colonized infants resulted from the error of catheterizing an infected site, followed by profusion with a highly irritating solution of 15% glucose.

Experience has demonstrated that the pustular lesions can be minimized, since they are related to the inoculum size of *S. aureus* 502A (TABLE 5). It can be seen that deliberate colonization with 2,000–4,000 bacteria results in a pustular rate of 1%. When a cotton swab technique is used, which results in

TABLE 5

PUSTULAR LESIONS RELATED TO INOCULUM SIZE OF *S. aureus* 502A

Authors	Number of Organisms	Method	Number of Newborns	Percentage of Newborns with Pustules
Shinefield et al.[21]	2×10^3 to 4×10^3	microburette	524	1.0
Light et al.[22]	2×10^3 to 5×10^4	cotton swab	584 *	<5.0
Light et al.[22]	2×10^3 to 5×10^4	cotton swab	687	3.5
Houck et al.[25]	2×10^3 to 5×10^4	cotton swab	644	4.7
Light et al.[23]	1×10^8	cotton swab	85	14.0
Blair and Tull [24]	1×10^8	cotton swab	50	34.0
Houck et al.[25]	?	cross infections	444	0.5

* 470 were full-term; 114 were premature.

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application of approximately 2,000–50,000 bacteria, the pustular rate is in the range of 5% while colonization with 1×10^8 bacteria results in a lesion rate of 14–34%.[22, 23] It should be noted that in a large group of infants who were cross-infected, the pustular rate was approximately 0.5%.[25] All the data suggest that small numbers of inoculated organisms minimize the pustular rate. Since colonization can be accomplished with relatively few bacteria, it would seem wise to colonize with about 5,000–10,000 502A during epidemics (TABLE 6).

The data substantiate the fact that artificial colonization of newborn infants with 502A in nursery situations in which there is a high colonization and disease rate due to a virulent hospital strain of staphylococcus is an effective and safe method for curtailing epidemics, provided that reasonable precautions are followed.[26]

Another situation in which the concept of bacterial interference has been useful is in the treatment of patients with recurrent furunculosis.[27–30] Here the technique has been one of recolonization rather than colonization. Prior to the nasal application of strain 502A, individuals with recurrent furunculosis are systemically treated with antibiotics and also with application of an antimicrobial cream to the nasal mucosa. This technique eliminates the staphylococcal carrier strain related to the disease and is necessary to assure effective nasal colonization with 502A.

FIGURE 1 and TABLE 7 outline a controlled study in which this technique was utilized.[31] It can be seen that about 80% of the individuals with recurrent furunculosis were cured. Additional data have been collected on approximately 600 patients over a 7-year period.[26] In this group of individuals, relapse or recurrence of the original staphylococcal strain on the nasal mucosa of treated individuals within 12 months was 21% (TABLE 8). A high relapse rate was noted in patients with diabetes, eczema, or acne. Of interest was the fact that the relapse rate was 15% in patients treated with a penicillin derivative, while patients who were suspected of penicillin allergy and treated with lincomycin exhibited a relapse rate of 45% (TABLE 9).

Disease associated with 502A was noted in 11 patients (TABLE 10). Three patients were diabetics and two had extensive eczema. To date there is only one case of recolonization associated with a 502A lesion that was classified as more than mild. This was a diabetic with pyarthrosis, which responded well to antibiotics. The patient had no further staphylococcal disease, despite numerous lesions prior to colonization.

Other workers reported lesions associated with the 502A strain of staphylococcus. An occasional pustule was seen by Maibach and colleagues.[28] Drutz and colleagues[32] reported that a patient with primary skin disease developed a 502A abscess while on steroids.

The importance of the nasal colonization status in patients with furunculosis is illustrated in a report of recolonization by Strauss and colleagues.[33] Three patients with recurrent furunculosis became free of furunculosis when recolonized by the standard technique. After a period of six months to a year, they were again noted to be nasal carriers of the original pathogenic strain. At this time, episodes of recurrent furunculosis related to the original carrier strain were again noted in all patients.

Recolonization is not helpful in all situations. After recolonization, no decrease was noted in the disease rate in an institution with a mild but chronic

TABLE 6
FREQUENCY OF TAKES * IN RELATION TO INOCULUM SIZE OF *S. aureus* 502A †

Authors	Method	Number of Organisms per Inoculum	Site of Inoculation	Number of Patients	Takes Number	Takes Percentage
Shinefield et al.[10]	microburette	2000–4000	nose	42	39	93
			umbilicus	42	30	72
Boris et al.[20]	microburette	2000–4000	nose	25	21	84
			umbilicus	25	23	92
Light et al.[21]	cotton swab moistened with broth containing 2.5×10^5/ml	estimated 2000–5×10^4	nose	584	530	91
			umbilicus	584	520	89

* Take indicates the presence of marker 502A strain 24 hours after inoculation.
† From Houck *et al.*[22]

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RELAPSES

Underlying Disease	R
Diabetes	
Eczema	
Acne	
Total relapse	

* From Shinefield

Dicloxacillin
Lincomycin
Total

* From Shinefield

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TABLE 7

SUMMARY OF COLONIZATION STATUS IN CONTROL AND INOCULATED FAMILIES DURING FIRST YEAR AFTER TREATMENT *

	Families	Individuals	Treated	Recurrence of Original Strains		Individuals with Lesions
				Number	Percentage	
Control †	12	51	42	31	74	15
Inoculated with 502A ‡	16	82	66	18	27	4

* From Boris *et al.*[31]
† Controls received antibiotic therapy and saline.
‡ Inoculated families received antibiotic therapy and 502A.

TABLE 8

RELAPSES IN 587 PATIENTS COLONIZED WITH *S. aureus* 502A *

Underlying Disease	Patients Treated	Relapsed
Diabetes	5	4
Eczema	3	3
Acne	11	5
Total relapse	122/587	21%

* From Shinefield *et al.*[20]

TABLE 9

RELAPSES IN RELATION TO INITIAL THERAPY *

	Total Treated	Relapse	
		Number	Percent
Dicloxacillin	470	69	15
Lincomycin	117	53	45
Total	587	122	21

* From Shinefield *et al.*[20]

From Houck *et al.*[32]

TABLE 10

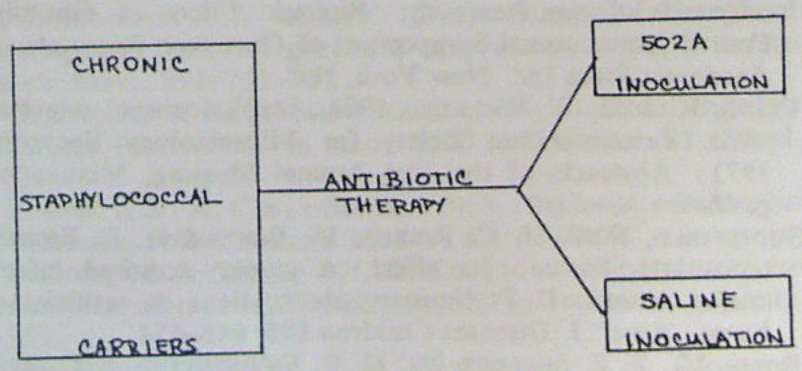
502A LESIONS IN 587 RECOLONIZED PATIENTS *

Lesion	Underlying Disease	Number of Patients
External otitis	diabetes	1
Impetigo	eczema	2
Pyarthrosis	diabetes	1
Pustules (1 or 2)	diabetes	1
	none	3
Stye	none	3
Total		11

* From Shinefield *et al.*[26]

staphylococcal problem.[3,4] Therefore utilization of this technique must be individualized with regard to patient and environment.

The mechanism responsible for this phenomenon in humans is not understood. The possibilities include the development of an unfavorable growth environment, as a result of initial colonization. This may result from production of inhibitors, creation of unfavorable pH or redox potential, accumulation of toxic metabolic products, or the production of an antimicrobial substance that may result in bacterial antagonism. Another possibility is that the colonizing strain depletes the environment of an essential nutrient and thus inhibits the growth of a second strain of a similar organism. As a matter of fact, the precise mechanism of interference between two staphylococcal strains has been determined in some experimental models. Ribble found that bacteria-free filtrate prepared from broth cultures of coagulase-negative staphylococci was less able to support the growth of coagulase-positive staphylococci than fresh broth.[1,2] He offered evidence that the mechanism of action in this *in vitro* model could be attributed to the production of a nonprotein, dialyzable, heat-labile substance. Primary action of the substance was to interfere with the utilization of an essential nutrient of the organism, niacinamide, and thus interfere with staphylococcal growth. It is of interest that when allantoic fluid is used instead of broth as a medium for bacterial growth, interference is the result of nutrient exhaustion, inasmuch as the addition of a combination of



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amino acids results in the restoration of the ability of filtrate to support the growth of coagulase-positive staphylococci.

The *in vivo* models that have been used to study the phenomenon of bacterial interference between two strains of staphylococci include fertile hen's eggs [3, 5, 6] and full-thickness burns of the skin of rabbits and guinea pigs.[8–9] Many interesting observations have been made in these models, but the exact mechanism of interference in these circumstances has not been completely understood.

It is clear that although the phenomenon of bacterial interference between strains of *S. aureus* has been subject to intensive investigation, there is no explanation for the well described observations in humans. Despite these limitations, some useful information and therapeutic tools have been developed. In at least two situations, nursery outbreaks of staphylococcal disease and recurrent furunculosis in humans, the host can be protected by deliberate implantation or manipulation of the flora of the upper respiratory tract.

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DR. S. MUDD: Dr. Sh
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DR. SHINEFIELD: No,

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DISCUSSION OF THE PAPER

DR. S. MUDD: Dr. Shinefield, have you looked at all into the relationship of delayed-type hypersensitivity and the phenomenon of bacterial interference that you have described? I suspect that there may be a factor here; at least, the turning on of the macrophages may be a factor.

DR. SHINEFIELD: No, we have not.