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"BACTERIAL INTERFERENCE" AND STAPHYLOCOCCIC COLONIZATION IN INFANTS AND ADULTS*

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Evidence has been presented previously to indicate that both naturally occurring or artificially induced colonization with staphylococci of the nasal mucosa of adults and the nasal mucosa and umbilical cord of infants interfere with the subsequent acquisition on these sites of other strains of staphylococci.[1-5] For lack of a better name, this phenomenon has been called "bacterial interference," although the mechanism of action remains obscure. It is the purpose of the present communication to summarize briefly the data bearing on bacterial interference which have been accumulated in the past several years.

Our attention was first directed to this phenomenon by two items of epidemiologic data. The first of these observations is summarized in TABLE 1. A nurse known to be a nasal carrier of *Staphylococcus aureus* type 80 81 had repeated contacts with 68 newborn infants of various ages. Among the group of babies handled by her during their first 24 hours of life, the colonization rate with *Staph. aureus* type 80 81 was 22 per cent, while of the 31 infants more than 24 hours old cared for by the same nurse carrier during the identical time period, none was found to be similarly colonized. A more detailed analysis indicated that 26 or 84 per cent of the infants more than 24 hours old were nasally colonized with coagulase-positive staphylococci other than type 80 81 prior to contact with the infectious nurse, while no baby less than one day of age was similarly infected. This observation suggested two possibilities: (1) Resistance to infection increases with age; (2) the presence of staphylococci interferes with the subsequent acquisition of another strain.

An epidemiologic experiment was thus arranged (TABLE 2). A group of newborn infants was admitted to a nursery (Nursery B) where colonization rates with staphylococci type 80 81 were relatively low (11 per cent). After

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TABLE 1
COLONIZATION OF BABIES WITH STAPHYLOCOCCUS 80/81 FOLLOWING CONTACT WITH A SINGLE CARRIER

Time of contact with carrier	Number of infants at risk	Number colonized with 80/81	%
1st day of life	37	8	22
After 1st day of life	31	0	0

(= Tabelle 1 Hf 584)

TABLE 2
COLONIZATION OF BABIES WITH STAPHYLOCOCCUS 80/81 IN TWO DIFFERENT NURSERIES

Babies, nursery A	18/32*	(56)
Babies, nursery B	4/36	(11)
Babies transferred from B to A after 16 hours	2/14	(14)

*Number colonized with 80/81 total number of babies (per cent).

(= Tabelle 2 · 584)

TABLE 3
NUMBERS OF STAPHYLOCOCCI, STRAIN 502-A NEEDED TO COLONIZE THE NASAL MUCOSE OF NEWBORN INFANTS LESS THAN 24 HOURS OLD

No. bacteria	No. infants inoculated	Successful takes (%)	
0-200	43	7	(16)
201-400	28	14	(50)
>400	11	9	(82)

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emaining in this nursery unit for 16 hours, the infants were transferred for a our- to five-day stay to a second nursery (Nursery A), where the 80/81 olonization rate ranged between 50 per cent and 60 per cent in infants admitted immediately after birth. The colonization rate with type 80/81 among he group transferred from Nursery B to Nursery A was found to be similar o the rate of colonization in newborn infants admitted directly into Nursery B. Therefore, the 16-hour stay in Nursery B conferred upon the infant a measurable degree of protection when exposed thereafter to an environment rich in staphylococci type 80/81. It is of interest that 80 per cent of the babies ed from Nursery B to Nursery A were found to be colonized before their transfer by coagulase-positive staphylococci other than type 80/81. This observation again suggests that staphylococci already implanted in the nose inhibit subsequent colonization by other strains.

TABLE 4
NUMBERS OF STAPHYLOCOCCI, STRAIN 502-A, NEEDED TO COLONIZE THE UMBILICUS OF NEWBORN INFANTS LESS THAN 24 HOURS OLD

(= table s (584)

No. bacteria	No. infants inoculated	Successful takes (%)
7, 8, 9	19	9 (47)
55	11	9 (82)

It is therefore reasonable to attempt to utilize the phenomenon of "interference" to prevent colonization of newborns by pathogenic types in situations where other measures of control had failed, provided a suitable "interfering" or "blocking" strain of staphylococcus could be found. Such an organism must possess certain properties: (1) It must not be associated with disease; (2) it should be capable of colonizing and then persisting for some time on the nasal mucosa and the umbilical stump of newborn infants; (3) it should be readily identifiable in the laboratory; and (4) it should be susceptible to penicillin and other nontoxic antimicrobial agents.

Our previous experience with a penicillin-susceptible staphylococcus of the phage type 7/47/53/81 (our strain 502-A) indicated that this organism possesses these requirements. Originally, the strain had been isolated from a nurse and subsequently from the nasal mucosa of many infants in our nurseries over a two-and-one-half-year period. During this interval, clinical and epidemiologic observations revealed a striking lack of staphylococcal disease among the colonized infants or their family contacts, despite close observation extending over several months.

TABLE 5
SITE AND NUMBER OF TAKES IN INFANTS INOCULATED WITH STRAIN 502-A

Site	Number inoculated	Take (%)	
Nose	123	110	(89)
Umbilicus	133	100	(75)

Information was obtained about the number of organisms required to infect consistently an infant's nose and umbilicus. Dilutions in isotonic saline of an 18-hour broth culture were made so that a known number of bacteria in a volume of 0.0005 ml. was dropped on the nasal mucosa or umbilical stump of alternate babies. The nasal mucosa of 50 per cent of newborn infants were colonized when the inoculum contained 200 to 400 staphylococci (TABLE 3). Eighty-two per cent were colonized when 400 or more bacteria were used. Colonization of the umbilicus was attempted in 30 newborn infants less than 24 hours old (TABLE 4). Colonization of the umbilical stump was accomplished in 47 per cent of these babies with as few as 7, 8, or 9 bacteria; 82 per cent of the patients were colonized with 55 bacteria.

Since no staphylococcal disease caused by strain 502-A was observed in these deliberately colonized infants or among their family contacts, it appeared reasonable to determine whether artificial colonization of newborn

TABLE 6
NASAL COLONIZATION WITH COAGULASE-POSITIVE STAPHYLOCOCCI OTHER THAN 502-A IN SUCCESSFULLY INOCULATED AND CONTROL INFANTS DURING HOSPITAL STAY (H) AND AT INITIAL FOLLOW-UP (F)

Category	Infants colonized with strain other than 502A Number (%)	
	H	F
Inoculated takes	5/108 (4.6)	7/93 (7.5)
Control	56/143 (39.1)	68/129 (52.7)

P = <0.001.

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infants would prevent infection and disease due to epidemic strains of staphylococci.

The data to be presented summarize observations made in nurseries in four separate areas of the United States: New York, Cincinnati, Atlanta, and Pineville, La. In each of these nurseries an outbreak was currently in progress, with high rates of staphylococcal colonization and disease in the infants and their families. The strains responsible for disease were staphylococci of phage type 80 81 or a related variant. Attempts to control these epidemics by a variety of means had proven unsuccessful.

Approximately one-half the infants in each nursery were artificially colonized. No other change was initiated in nursery procedure. Personnel who carried epidemic strains were permitted to work and were not notified of their

TABLE 5

UMBILICAL COLONIZATION WITH COAGULASE-POSITIVE STAPHYLOCOCCI OTHER THAN 502A IN SUCCESSFULLY INOCULATED AND CONTROL INFANTS DURING HOSPITAL STAY BY SEX IN TOTAL FOLLOW-UP

Category	Number	Infants colonized with strain other than 502A	
		Number	%
Inoculated takes	M 58	5	(5.2)
	F 55	2	(2.4)
Control	M 148	75	(50.7)
	F 133	45	(33.8)

$p < 0.001$.

colonization status. Artificial colonization of infants was accomplished within two hours after birth by placing a known number of organisms of strain 502-A in a 0.0005 cc. drop on both sides of the nasal mucosa and on the umbilicus at the skin junction. In later epidemics, infants were reinoculated at age 12 hours at both of these sites.

TABLE 5 presents the number of infants with successful inoculations or "takes." A "take" was defined as the presence of marker strain 502-A at the inoculated site detected by culture 24 hours after inoculation. Among the 123 infants in whom artificial nasal colonization was attempted, this was accomplished in 89 per cent; there were umbilical takes in 75 per cent.

TABLE 6 demonstrates nasal colonization rates with coagulase-positive staphylococci other than strain 502-A in control and inoculated take infants

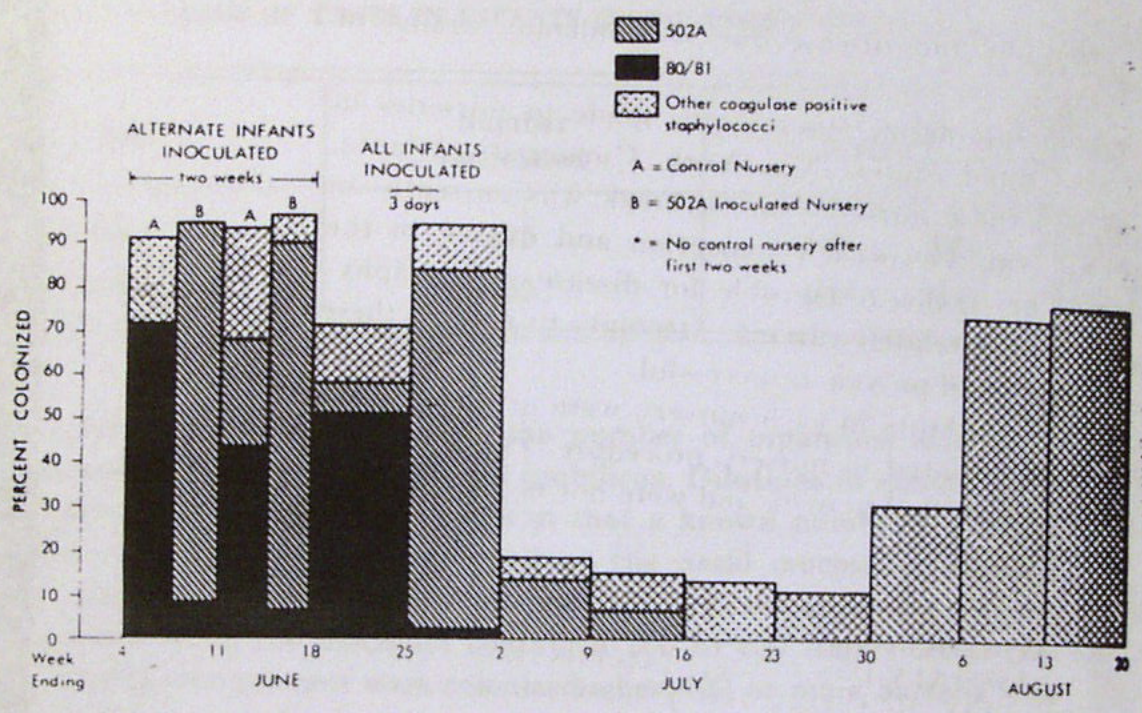

FIGURE 1. Influence of deliberate colonization with *Staph. aureus* strain 502-A on a nursery epidemic.

during the hospital stay and at the initial home follow-up visit when the infant was three to five weeks old. Of the 108 infants with successful takes of strain 502-A, 4.6 per cent became colonized with strain 80/81 or another coagulase-positive staphylococcus during the hospital stay. In contrast, in the control group of 143 infants, 56 or 39.1 per cent became spontaneously colonized with type 80/81 or a coagulase-positive staphylococcus other than strain 502-A.

The difference in colonization rates in the inoculated take and control infants was still apparent during the initial follow-up visit and is significant at a level of $P = 0.001$.

TABLE 7 shows similar data for umbilical colonization rates, and again a highly significant difference is observed.

FIGURE 1 demonstrates the results of surveillance of one nursery before, during, and after artificial colonization. Inoculated and control infants in this particular epidemic were kept physically separated but were cared for by the same group of nurses. The inoculated babies were maintained in Nursery B, and the control infants in Nursery A during the first two weeks of the observation. A very significant decrease in 80/81 colonization rates in the inoculated infants was observed. After two weeks, artificial colonization was temporarily halted, and the 80/81 rate in the two nurseries again rose to high levels. All newborn infants delivered over a three-day period were then artificially colonized with strain 502-A immediately after birth

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Concurrent with this procedure, staphylococcus type 80/81 disappeared from both nurseries and could not be recovered from infants at discharge. Six weeks after artificial colonization procedures had been terminated, 80 per cent of the infants were again spontaneously colonized, this time with a nontypable coagulase-positive staphylococcus. The results observed in the other three epidemics were entirely similar; each time a highly significant decrease in type 80/81 colonization rates was observed in the inoculated infants, and the outbreak could be terminated at will.

TABLE 8 demonstrates the relationship of the type of staphylococcus carried in the infant's nose to the development of lesions in him and his mother during a 24-week follow-up period. Twenty-seven infant and maternal lesions occurred among 53 infants colonized with type 80/81. The gross lesion rate in infants colonized at birth with strain 502-A was 8 per cent (10 out of 132), but this strain was in fact not responsible for most of the lesions. Strain 502-A was isolated from minor lesions only three times and in conjunction with type 80/81 once. Only staphylococcus type 80/81 was isolated from four other lesions in the 502-A inoculated babies.

These data support the conclusion that strain 502-A is relatively avirulent. A number of events which might increase the possibility of staphylococcal disease subsequently occurred in some of the 502-A colonized infants. For example, at least seven of the babies underwent major operations, including cardiac surgery and repair of a tracheoesophageal fistula. No staphylococcal complications were observed in these infants.

TABLE 8
RELATIONSHIP OF STRAIN OF STAPHYLOCOCCUS IN INFANT NOSE TO DEVELOPMENT OF DISEASE

	Lesion	80/81	502-A
Infant	Conjunctivitis	4 (4)	4 (3)
	Impetigo	16 (10)	1 (1)*
	Abscess	1 (1)	2 (2)*
	Omphalitis	1 (1)	0 (0)
Maternal	Abscess	4 (4)	2 (2)*
	Mastitis	1 (0)	1 (0)
	Total	27/53 51%	10/132 8%

*80/81 isolated.

P = <0.001.

Number of lesions from which *Staph. aureus* was recovered is indicated in parentheses.

TABLE 9
TYPES OF ORGANISMS PRESENT ON NASAL MUCOSA RELATED TO SUCCESSFUL TAKES* IN 78 INFANTS OVER 24 HOURS OLD; INOCULUM 500 OR MORE BACTERIA

	Total no. infants	Type of organism					
		Other than staph		Coag. neg. staph		Coag. pos. staph	
		Present	Absent	Present	Absent	Present	Absent
Take	68	38	30	28	40	0	68
No. take	10	7	3	8	2	4	6
		$X_2 = 0.31$;	P = 0.62	$X^2 = 4.04$;	P = 0.05	$X^2 = 13.88$;	P = 0.001

*Presence of marker 502-A strain detected at 24 hours after incubation.

A number of other babies similarly colonized developed viral respiratory infections subsequently, and six of these were hospitalized with bronchiolitis or bronchitis. In no case was the respiratory disease related to the staphylococcus, and in none of the infants did the illness progress to staphylococcal pneumonia.

These epidemics also provided additional data to support the concept of bacterial interference. TABLE 9 presents an analysis of success and failure of artificial colonization related to the prior presence or absence of certain bacteria in the nose. A striking relationship exists between the prior presence of *Staph. aureus* and the failure to implant the 502-A strain. Coagulase-negative staphylococci exert a much weaker effect. Similar data are available for the umbilical site with essentially identical results.

When the mothers of the artificially colonized infants were followed to determine whether or not they would acquire their baby's staphylococcus, it was noted that the prior presence of a coagulase-positive staphylococcus

TABLE 10
RELATIONSHIP OF PRIOR COLONIZATION STATUS TO SUBSEQUENT ACQUISITION OF INDEX BABY'S *STAPH. AUREUS* AMONG MOTHERS

Prior colonization status	Number of mothers	Number of Mothers colonized with infant's strain	Per cent of mothers colonized
Staph. aureus present	38	3	7.9
Staph. aureus absent	92	41	44.6

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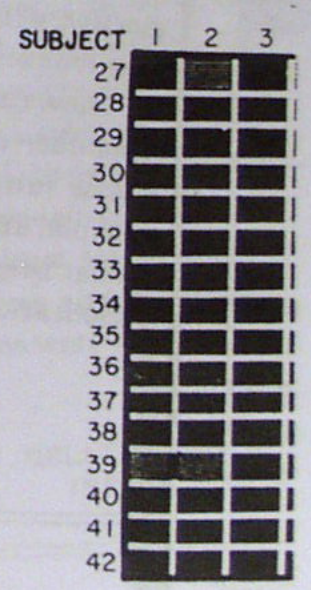

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blocked the acquisition of the new strain, while those adults without a staphylococcal flora appeared quite susceptible (TABLE 10). These data therefore indicate that the phenomenon of bacterial interference is not limited to the newborn but operates also in the adult.

These observations led to several other studies. The first of these was an attempt to determine whether it was possible to replace an existing flora in an adult with strain 502-A and to protect him against subsequent challenge with type 80/81.

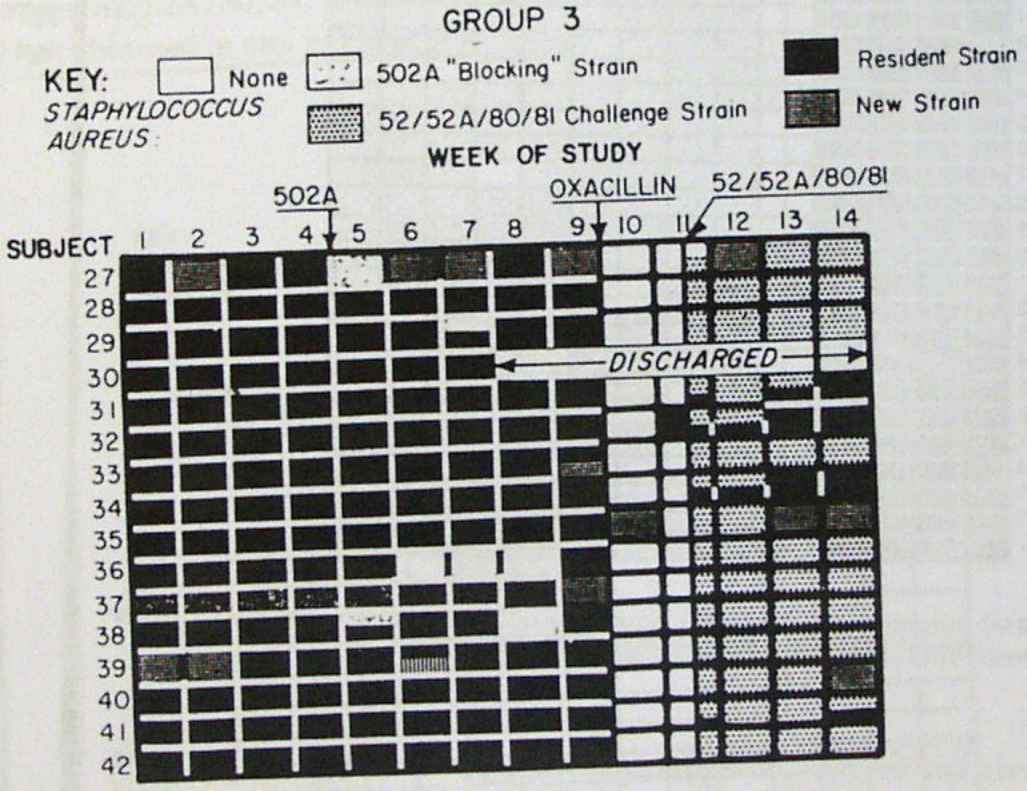

FIGURE 2. Nasal colonization with two *Staph. aureus* strains in persistent carriers before and after oxacillin therapy (see text).

Two independent series of observations were made. In each, the subjects were divided into groups of persistent nasal carriers and persistent nasal noncarriers of *Staph. aureus* on the basis of four or five consecutive weekly cultures. Artificial colonization of the nasal mucosa was attempted in some of the volunteers in each of these groups using two strains of *Staph. aureus*. One of the strains used was strain 502-A, arbitrarily defined as the blocking strain. The other was a penicillin-resistant staphylococcus phage type 52/52A/80/81, arbitrarily called the challenge strain. Volunteers from a penitentiary were selected for one study and first-year medical and nursing students for the other.

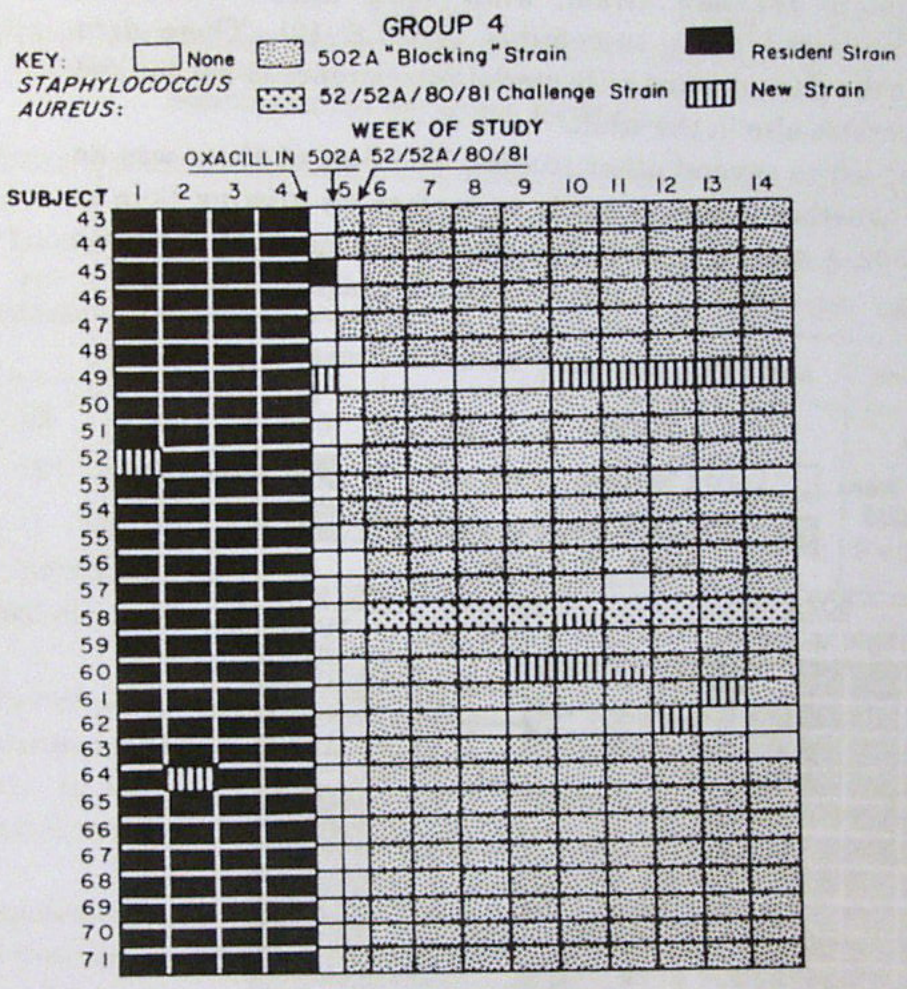

FIGURE 3. Nasal colonization with two *Staph. aureus* strains in persistent carriers before and after oxacillin therapy (see text).

(A) Sixteen persistent carriers of *Staph. aureus* were inoculated with strain 502-A three times over a four-day period (FIGURE 2). Each dose consisted of 10^6 bacteria placed on both nares. The only evidence of takes in this group of volunteers was the transient appearance of strain 502-A in two subjects. After nine weeks of surveillance, 15 of these same volunteers were treated for seven days with both local and systemic oxacillin. After completion of therapy, they were challenged intranasally with a single dose of 4×10^4 *Staph. aureus* type 52/52A/80/81. The challenge strain was subsequently isolated from all members of this group and persisted in 10 of the 15 for four weeks.

(B) Another group of 29 persistent carriers received systemic and local oxacillin therapy for one week (FIGURE 3). After this form of therapy, the original strain of *Staph. aureus* was recovered from only one patient. A new *Staph. aureus* type was recovered from the nasal mucosa of one additional individual in this group. All 29 volunteers were then challenged with strain 502-A, and takes were obtained in 27 of the 29 subjects (93 per cent). Twelve of the 27

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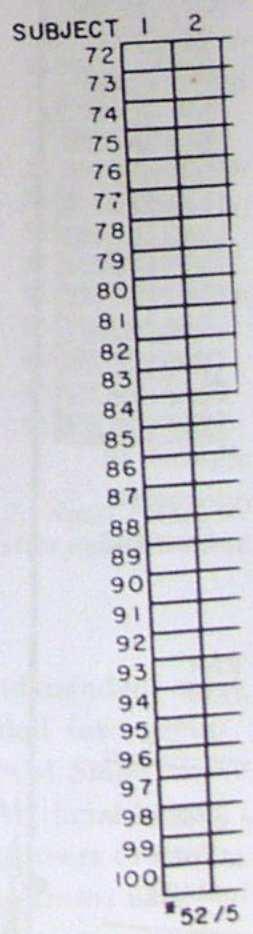

FIGURE 4. Nasal col
(see text).

volunteers successfully colonized were selected at random and challenged with a single 4×10^4 dose of type 52/52A/80/81. This time only one person had a take with the latter strain, but this patient had lost his 502-A strain prior to challenge. It may be concluded that strain 502-A confers a high degree of protection even against a large dose of directly implanted staphylococcus type 80/81.

Another group of volunteers consisted of 29 persistent noncarriers who were challenged with strain 502-A (FIGURE 4). Only 18 of the 29 (or 62 per cent) were colonized after three doses of 1×10^6 *Staph. aureus*. One week later, eight of the 18 members of this take group were challenged with type 52/52A/80/81. Successful colonization with the challenge strain was not obtained in any of these volunteers.

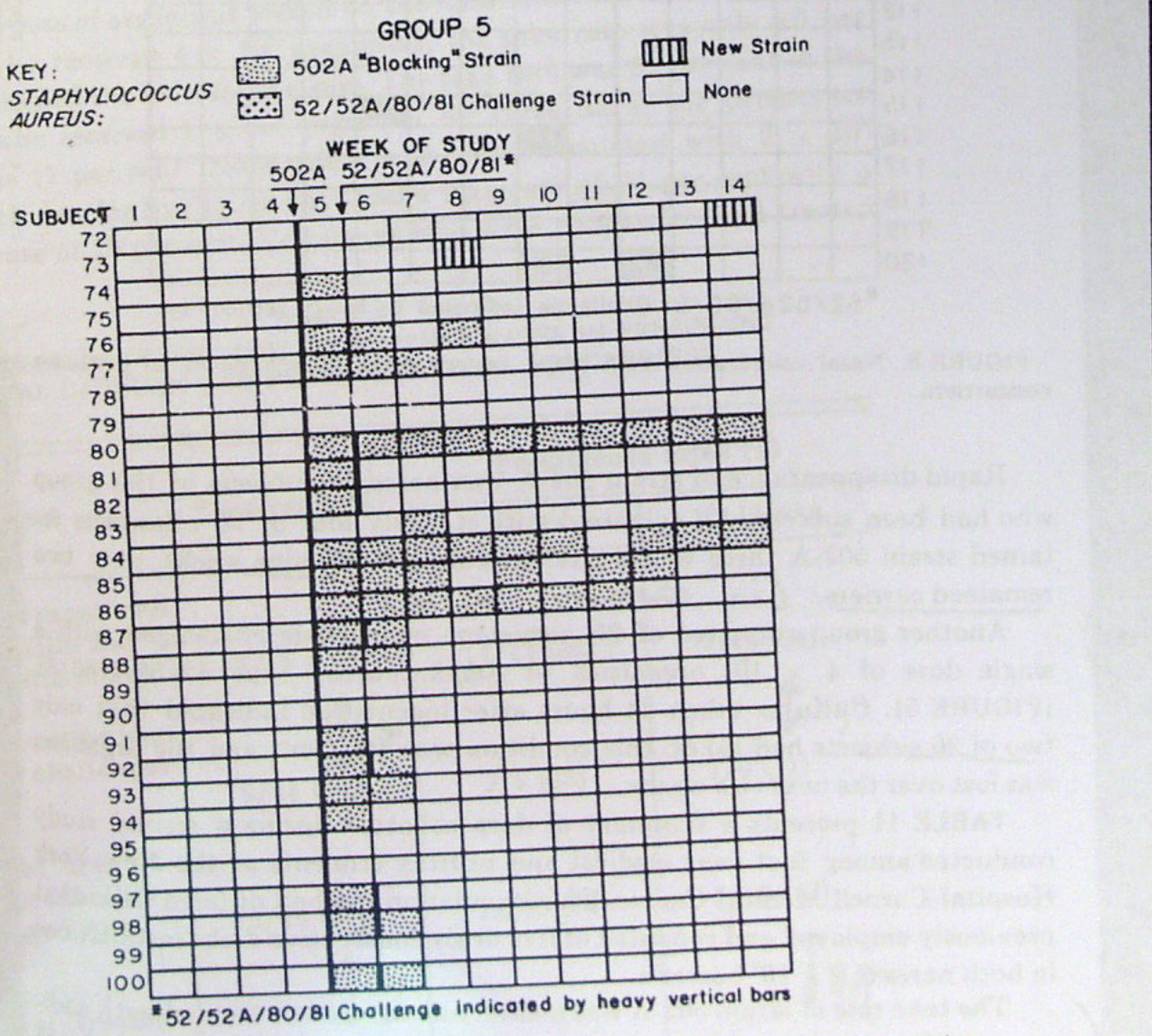

FIGURE 4. Nasal colonization with two *Staph. aureus* strain in persistent noncarriers (see text).

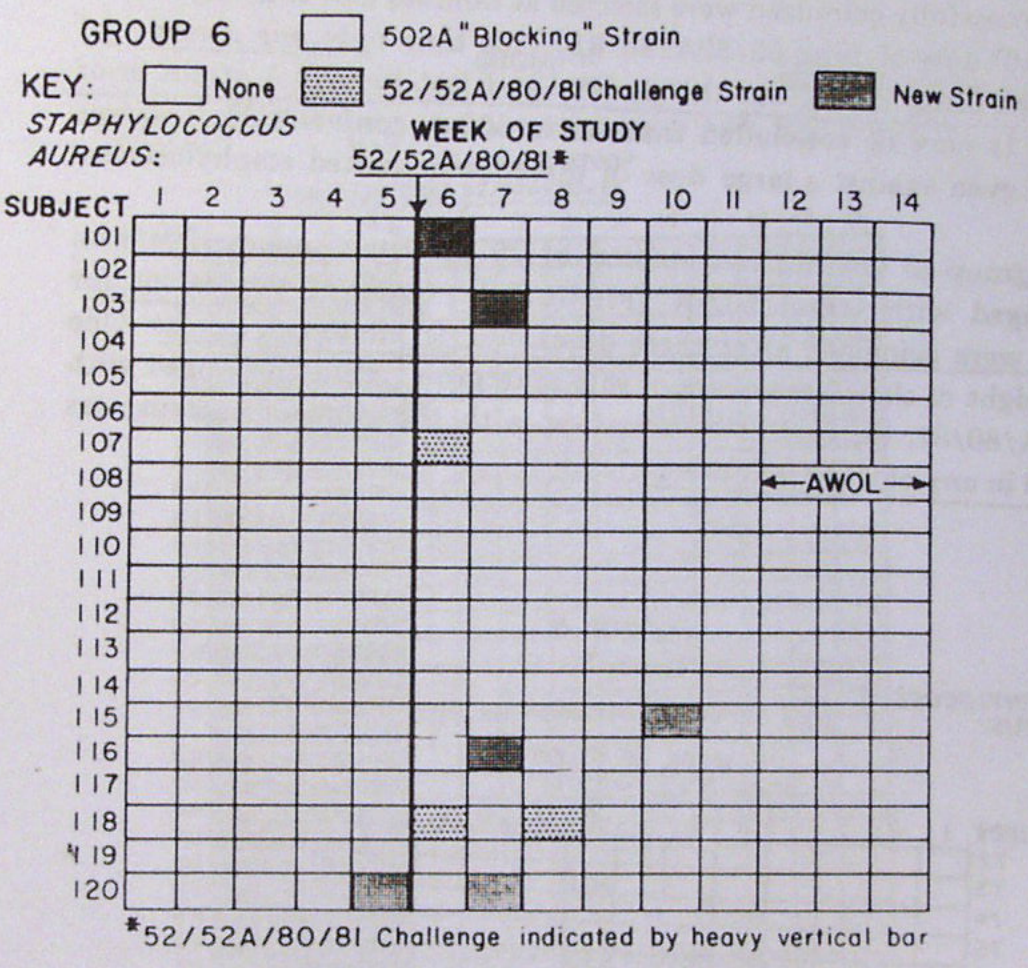

FIGURE 5. Nasal colonization with *Staph. aureus* type 52/52A/80/81 in persistent noncarriers.

Rapid disappearance of strain 502-A was noted in subjects of this group who had been successfully colonized with it. Only four of 18 volunteers retained strain 502-A three weeks after inoculation. At nine weeks, only two remained carriers.

Another group consisted of 20 persistent noncarriers challenged with a single dose of 4×10^4 organisms of *Staph. aureus* type 52/52A/80/81 (FIGURE 5). Cultures taken 24 hours after inoculation indicated that only two of 20 subjects had takes; this condition was transient and the organism was lost over the next two weeks.

TABLE 11 presents a summary of data collected during a second study conducted among first-year medical and nursing students at the New York Hospital-Cornell Medical Center. The inoculation method differed from that previously employed and consisted of five or six consecutive daily installations in both nares of 2×10^6 bacteria.

The take rate of strain 502-A was greater among carriers treated with sodium oxacillin than among carriers treated with a placebo and then inoculated with 502-A. Only three of nine of these placebo-treated carriers retained the

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Subjects
Carriers: treated with sodium oxacillin and challenged with 502-A
Carriers: treated with placebo and challenged with 502-A
Noncarriers: treated with sodium oxacillin and challenged with 502-A
Noncarriers: treated with placebo and challenged with 502-A

strain for more than three weeks. It is of interest that all three of these carriers had spontaneously lost their original resident strain before inoculation with 502-A was begun. The persistence rate at 13 to 14 weeks was greater in the group of individuals treated with oxacillin and challenged with 502-A than in the placebo 502-A group.

Take rates between the two noncarrier groups were not significantly different (94 per cent and 83 per cent), almost the same as the take rates seen in carriers treated with oxacillin and challenged with 502-A. However, three weeks after antibiotic treatment was stopped, the persistence of 502-A was significantly higher in noncarriers who had received oxacillin than in subjects who did not receive antibiotics before inoculation. This difference persisted throughout the 13 to 14 weeks of the follow-up period.

TABLE 12 compares take and persistent rates in the four groups of noncarriers in both studies. The take rate in the noncarriers appears to be directly related to the dose of organisms placed on the nasal mucosa. Thus, among the first group who received 4×10^4 organisms, the take rate was only 10 per cent; none retained the inoculated strain. The take rate was 62 per cent in the noncarriers who received 1×10^6 organism for three days; the persistence rate here was 17 per cent. Noncarriers who were inoculated with 2×10^6 organism each day for five to six days had a take rate of 94 per cent with a persistence rate of 29 per cent. Volunteers who were noncarriers and treated

TABLE 11
COMPARISON OF "TAKE" AND PERSISTENCE RATES IN PERSISTENT NASAL CARRIERS AND PERSISTENT NASAL NONCARRIERS

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

with local and systemic oxacillin before inoculation with 2×10^6 organisms for five to six days showed a take rate of 83 per cent as well as the highest persistence rate of the four groups.

In summary, these latter data indicate that heavy colonization of the nasal mucosa with strains of *Staph. aureus* in adults interferes with subsequent colonization by other *Staph. aureus* strains, much as it does in infants. This capacity to interfere is not restricted to a single *Staph. aureus* type. The resistence to colonization by a second *Staph. aureus* appears to depend partly on the local presence of large numbers of resident staphylococci, since removal or suppression of this original organism renders the nasal mucosa increasingly susceptible to artificial colonization with other strains. These data also suggest that factors exist other than the mere physical presence of staphylococci which interfere with attempts to colonize the nasal mucosa. These unknown protective factors can be suppressed by antimicrobial therapy or they can be overwhelmed by the repeated administration of large doses of *Staph. aureus*. The mechanism responsible for these phenomena awaits further study.

TABLE 12
COMPARISON OF TAKE AND PERSISTENCE RATES IN FOUR GROUPS OF NONCARRIERS (6)

Group	Number of organisms	Number in group	Takes (%)	Persistence at 9 weeks (%)
Noncarrier No Rx	1 day: 4×10^4	20	2 (10)	0 (0)
Noncarrier No Rx	3 days: 1×10^6	29	18 (62)	3 (17)
Noncarrier No Rx	5-6 days: 2×10^6	18	17 (94)	5 (29)
Noncarrier Oxacillin	5-6 days: 2×10^6	18	15 (83)	7 (47)

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Discussion

PAUL F. WEHRLE: Dr. Eichenwald, I think these are beautifully done, elegant studies. I wonder if you would care to make a statement about whether the procedure of inoculating 502-A is to be recommended as a general procedure in, first, epidemic situations or, secondly, in interepidemic or endemic situations. If you have reservations about this, what might they be?

A second question is: What do you think about the possible risk of a simultaneous viral respiratory infection to infants artificially inoculated in this way?

H. F. EICHENWALD *(The University of Texas, Southwestern Medical School, Dallas, Texas):* To answer the first question, I personally do not believe in any routine prophylactic administration of anything in newborn infants during situations when there are no epidemics, when the infants are well, and when no pathogenic type staphylococci are present. This would include the use of germicidal soaps, ointments, or 502-A.

Our data indicate very clearly that during the presence of a severe epidemic of staphylococcal disease, the use of 502-A represents the most immediate, safest and effective method of terminating the epidemic. I feel that we now have enough data, involving several thousand babies, to indicate that this is a completely safe procedure.

The only reason I would have reservations about inoculating infants routinely with stain 502-A is because we do not know what time will hold for it. We know it is possible that 502-A may change, although in the years that we have proceeded with these studies, we have noted no detectable changes of any sort.

As far as the second question is concerned, I did mention in the paper that a number of infants who had colonization with 502-A had relatively severe lower respiratory tract viral infections, such as bronchiolitis, which as you know is a form of viral pneumonia. These infants did not develop staphylococcal pneumonia despite the fact that they were not treated specifically to eradicate the 502-A. In other words, we have no evidence that the presence of viruses would potentiate a severe staphylococcal pneumonia in these babies.

It's of interest, for those of you who are not pediatricians, that practically all staphylococcal pneumonias seen these days are associated with the presence of a "virulent" or pathogenic staphylococcus and are often associated with a viral infection, but apparently it takes a potentially pathogenic staphylococcus and a virus to cause the severe type of lower respiratory tract disease we call staphylococcal pneumonia.

WEHRLE: Do you have any information in the use of this 502-A in treatment of adults with perineal carriage?

EICHENWALD: No, we have none.

ARTHUR C. WHITE *(Medical College of Georgia, Augusta, Ga.)*: Do you have any idea of the relative rates of growth in the nose of these two organisms, Dr. Eichenwald? What quantities of 502-A may be in the nose compared with 80/81?

EICHENWALD: I can say that despite attempts to try to quantitate the numbers of organisms, we have not been able to do this with sufficient consistency to warrant giving an answer that would have any degree of reliability.

WEHRLE: I think it's of interest that the only clinical lesions that you have seen in association with this particular strain have been connected with conjunctivitis. Is that not correct? And how do you feel as to its having an etiologic role as far as conjunctivitis is concerned? Do you have any comments?

EICHENWALD: Conjunctivitis in infants is a very common occurrence and many conjunctivities, as I think most pediatricians know, are in fact sterile. Whether the organism was etiologically related to the appearance of the conjunctivitis, we do not know. All we can say is that the organism was present at the time and possibly, therefore, it was related to the appearance of the conjunctivitis. But whether there is a true cause and effect relationship we do not know.

WEHRLE: Is there any further discussion? Thanks very much, Dr. Eichenwald.