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Interactions of Staphylococcal Colonization

Influence of Normal Nasal Flora and Antimicrobials on Inoculated Staphylococcus aureus Strain 502A

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IT HAS BEEN clearly demonstrated that artificial colonization of the nasal mucosa of newborns with one strain of *Staphylococcus aureus* interferes with subsequent acquisition of a second strain of *S aureus*.¹ This deliberate colonization of infants shortly after birth with a staphylococcal strain of low virulence (strain 502A) has been employed to protect infants from colonization and disease with virulent epidemic strains of *S aureus*.²⁻⁶

Following these observations, studies were extended to two groups of adults. Observations on one group (male, adult volunteers, members of the Federal Penitentiary in Atlanta) emphasized altered resistance of carriers to nasal colonization following administration of sodium oxacillin.^{7,8}

The present observations were made on medical and nursing students at the New York Hospital-Cornell Medical Center pri-

marily to study colonization of oxacillin- and placebo-treated noncarriers by a selected strain of *S aureus*. Data were also collected on the effect of sodium oxacillin on organisms other than *S aureus* carried on the nasal mucosa. In addition, the protection which deliberate *S aureus* inoculation afforded the host against reinfection by other microbes was also evaluated.

Definitions

The following terms were arbitrarily defined:

Carrier.—An individual from whose nose a strain of *S aureus* was recovered at least three times from four consecutive weekly cultures.

Noncarrier.—An individual from whose nose no *S aureus* was recovered at least three times over the same period.

Challenge Strain of *S aureus*.—A penicillin-sensitive, non-penicillinase producing, coagulase-positive strain of *S aureus* of low virulence—called strain 502A.

Criteria of Successful Inoculation or "Take".—Isolation of 502A from nose by culture 24 hours after inoculation.

Resident Strain.—Original strain of *S aureus* recovered from carriers during the initial culture period.

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Materials and Methods

The nasal mucosa of 81 first-year medical students and 87 first-year nursing students was cultured for four consecutive weeks. Of the combined total of 168 students, all the noncarriers who volunteered (38 students) participated in the study. Only carriers who volunteered who harbored a strain that could be differentiated easily from the challenge strain were participants in the study (45 students).

Carriers were then randomly subdivided into three smaller groups as were noncarriers. One group of carriers and one group of noncarriers received sodium oxacillin followed by nasal inoculations of saline. A second group of carriers as well as a second group of noncarriers received sodium oxacillin followed by nasal inoculations of *S aureus* strain 502A. The third group of carriers and the third group of noncarriers both received placebo capsules followed by nasal inoculation of *S aureus* 502A (Table 1).

The carriers and noncarriers, treated with sodium oxacillin, took 2 gm by mouth, three times a day, one hour before or two to three hours after meals for seven consecutive days. The antibiotic was, at the same time, applied locally to the nasal mucosa by means of cotton swabs saturated with sodium oxacillin ointment, containing 10 mg of sodium oxacillin per gram of grease base. An attempt was made to cover the mucosa to a depth of 3 cm from the nostrils. For those who did not receive the sodium oxacillin, an equivalent amount of placebo was administered in the same manner.

Within 24 hours after cessation of antibiotic administration, 2×10^8 organisms were placed, by means of a microburet, in each nostril of participants in groups challenged with 502A five to six times over the next seven days. Those not challenged with 502A received an equivalent amount of saline in an identical manner during the same period of time.

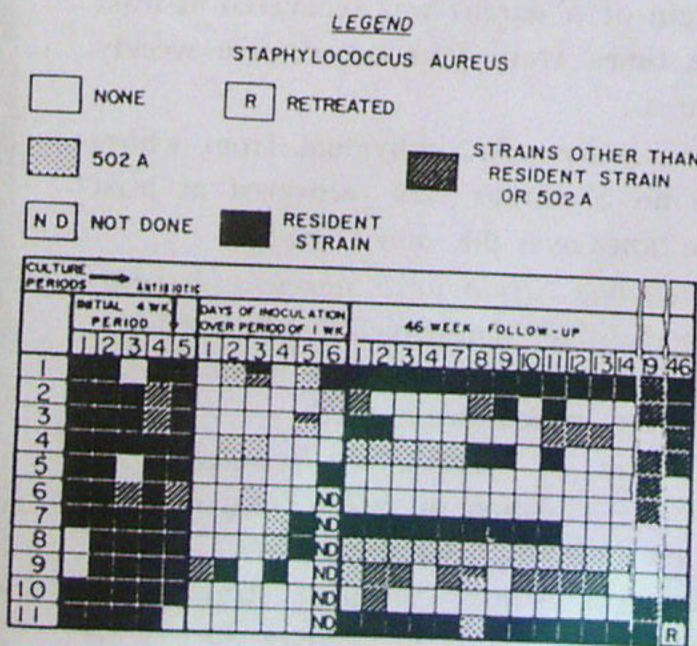


Fig 1.—Medical students and nurses, group 1: Carriers receiving sodium oxacillin and saline.

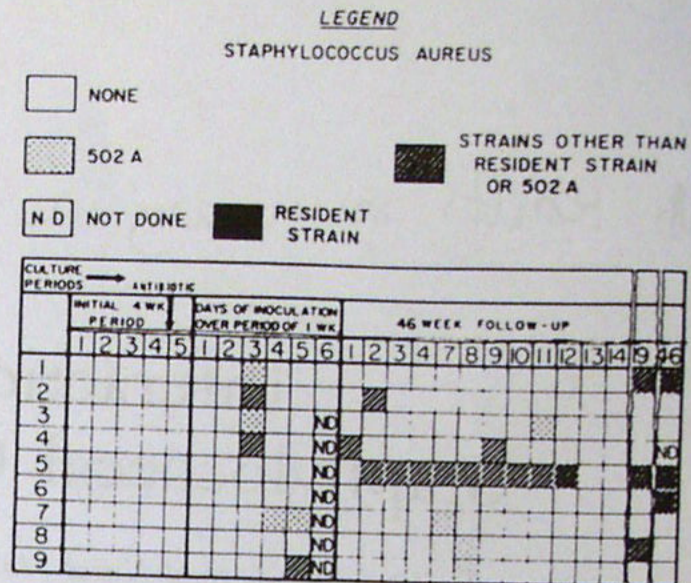


Fig 2.—Medical students and nurses, group 2: Noncarriers receiving sodium oxacillin and saline.

Nasal cultures were obtained from all participants just prior to each inoculation of 502A or saline and at weekly intervals for 14 weeks following the cessation of 502A or saline administration. No cultures were taken the fifth and sixth week after inoculation because students were on vacation. Additional cultures were taken 19 and 46 weeks after inoculation. Dry, sterile, cotton applicators were rotated three times in each nostril and immediately placed in a tube containing 0.5cc of sterile trypticase soy broth. Within two hours each applicator was streaked on three agar plates: trypticase soy agar, mannitol agar, and sheep blood agar. Following 48 hours of incubation at 37 C, all bacterial colonies were identified by inspection and classified as follows: *S aureus*, *Micrococcus*, *Neisseria*, diphtheroid, coliform, *Proteus*, *Pseudomonas*, *Pneumococcus*, *Streptococcus*, *Haemophilus influenzae*, and yeast. Three colonies from each plate showing the typical morphology, color, and consistency of staphylococcal colonies were phage typed. Those not lysed by

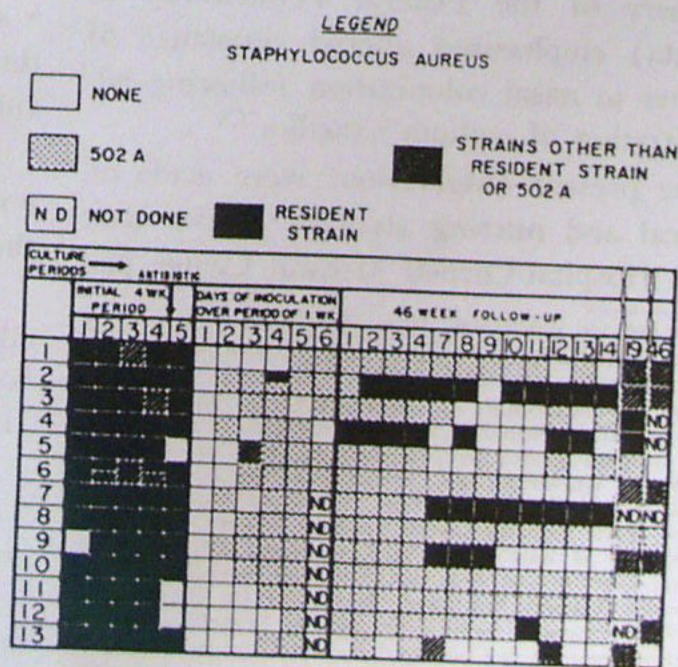


Fig 3.—Medical students and nurses, group 3: Carriers receiving sodium oxacillin and 502A.

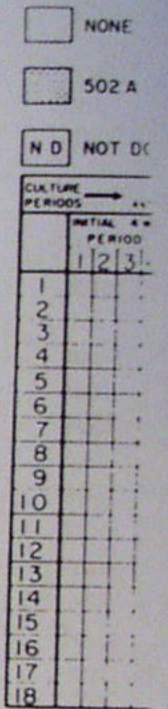


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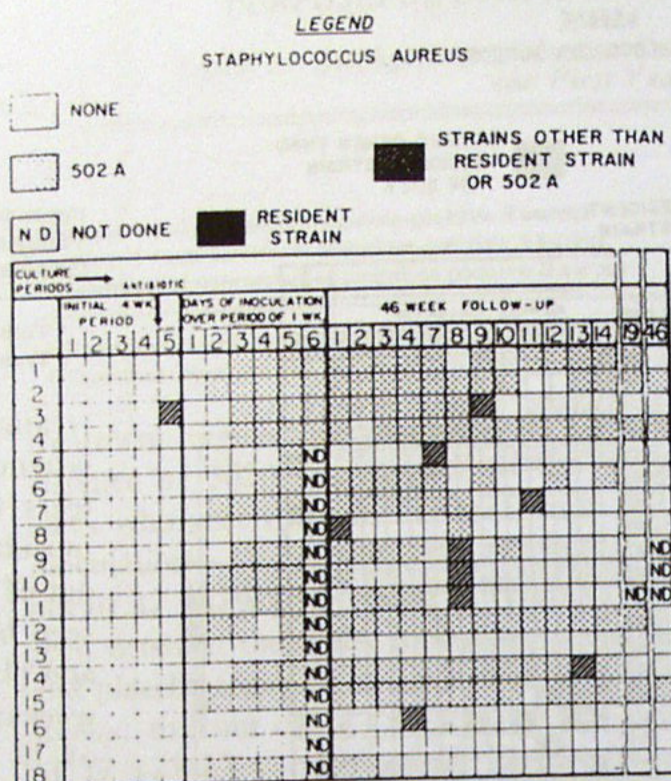


Fig 4.—Medical students and nurses, group 4: Noncarriers receiving sodium oxacillin and 502A.

phages were tested for the presence of coagulase using a modification of the slide agglutination method of Cadmen and Graves.⁹ Coagulase negatives were then considered as a form of *Micrococcus*.

Results

Of the 168 students originally cultured, 54 (32%) were persistent carriers, 69 (41%) were persistent noncarriers, and 45 (27%) carried *S aureus* intermittently (Table 2). Of the carriers, 14 (26%) had penicillin-resistant strains of *S aureus*.

The 11 carriers in group 1 were treated with sodium oxacillin and challenged with saline (Fig 1). During the week when saline was inoculated, the original strains were recovered in only seven of 60 cultures. During the 14-week follow-up, however, either the original strain or a new strain was recovered from the majority of individuals, ie, nine out of 11, or 82%. Of interest is the number of individuals who picked up 502A spontaneously (four out of 11 or 36%). Participant 8 became a persistent carrier of 502A. At 46 weeks three volunteers continued to carry their resident strain.

In group 2 the nine noncarriers were treated with sodium oxacillin and challenged with saline (Fig 2). Only one volunteer (No. 5) was spontaneously colonized and became a persistent *S aureus* carrier during

TABLE 1.—Experimental Design

Group	Carrier or Noncarrier	Treatment Regimen
I	Carrier	Sodium oxacillin + saline
II	Noncarrier	Sodium oxacillin + saline
III	Carrier	Sodium oxacillin + 502A
IV	Noncarrier	Sodium oxacillin + 502A
V	Carrier	Placebo + 502A
VI	Noncarrier	Placebo + 502A

the first 14 weeks of the follow-up. Subject 1 became an *S aureus* carrier at 19 weeks and still carried an identical strain at 46 weeks.

Group 3 consisted of 13 carriers treated with sodium oxacillin and challenged with 502A (Fig 3). Not only was there marked suppression or elimination of the original strains during the week of 502A inoculation (only one culture yielded the original strain), but all 13 members acquired 502A. Four weeks later, 11 out of 13 or 85% still carried the challenge strain. However, this persistence declined gradually over the next 15 weeks, so that on the culture 19 weeks after inoculation only four of 11 (36%) still carried 502A. At 46 weeks two of the ten volunteers still available for culture carried 502A.

Group 4 consisted of 18 noncarriers treated with sodium oxacillin and challenged with 502A (Fig 4). Of the 18 subjects, 15 (83%) acquired 502A during the inoculation period, at the four-week follow-up, 11

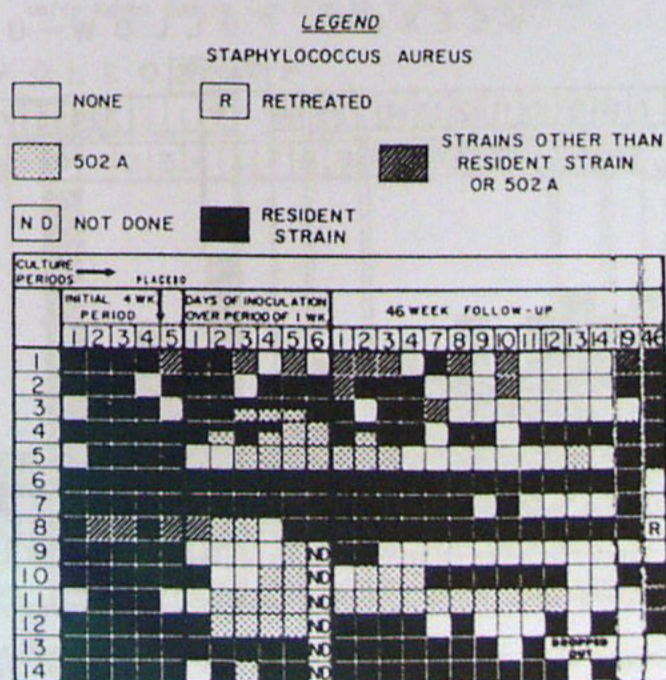


Fig 5.—Medical students and nurses, group 5: Carriers receiving placebo and 502A.

of the 15 (73%) still carried the organism, and by 19 weeks, the number of carriers had decreased to five out of 14 (36%). At 46 weeks three out of 12 members in this group still carried 502A.

Group 5 consisted of 14 carriers treated with placebo and challenged with 502A (Fig 5). Nine volunteers picked up 502A during the week of inoculation. However, only three participants, subjects 5, 10, and 11, carried the organism longer than one week, and these same individuals did not carry any strain of *S aureus* for at least two days before 502A could be detected. By 19 weeks none of these carriers were colonized with 502A. However, nine out of 14 students still carried some type of *S aureus* other than 502A at 46 weeks.

Group 6 consisted of 18 noncarriers who were given placebo and challenged with 502A (Fig 6). The "take" rate was striking (17 out of 18 or 94%). However, persistence of 502A declined sharply, and there were only eight of 17 (47%) carriers of 502A at four weeks. This rate remained about the same over the next ten weeks but at 19 weeks only one out of 17 or 6% still carried 502A. None carried 502A at 46 weeks.

The comparison of "take" and persistence rates among groups challenged with 502A is demonstrated in Table 3 and Fig 7 and 8. The "take" rate of 502A was greater among

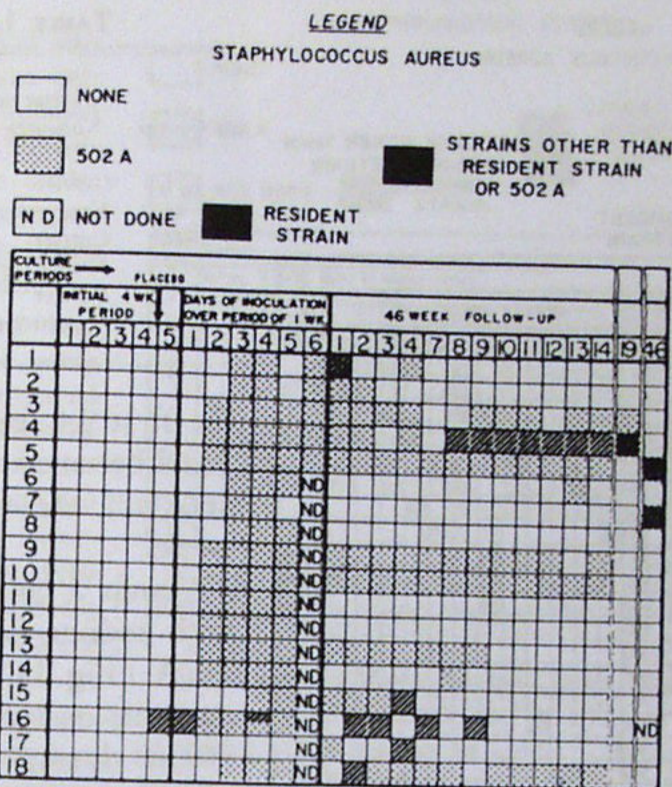


Fig 6.—Medical students and nurses, group 6: noncarriers receiving placebo and 502A.

carriers treated with sodium oxacillin (group 3), 13 of 13 or 100%, than among carriers treated with placebo (group 5), 9 of 16 or 64%. The persistence rate at four weeks was greater in group 3, 11 of 13 (85%), than in group 5, 2 of 9 (22%), and this difference persisted throughout the 46-week period of observation. The difference in "take" rates between the two noncarrier groups is not statistically significant, 15 of 18 (83%) for group 4 vs 17 of 18 (94%) for group 6. However, four weeks after

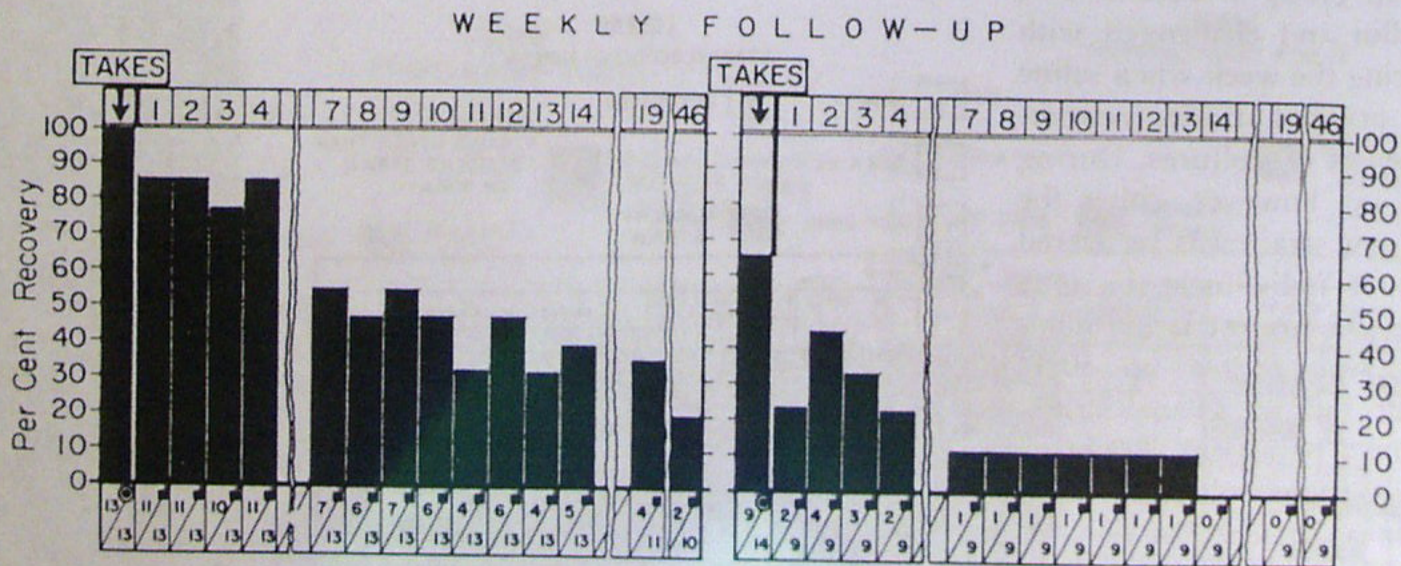


Fig 7.—Comparison of acquisition and persistence of 502A in carriers treated with sodium oxacillin and 502A with carriers treated with placebo and 502A.

TABLE 2

Persistent nasal carriers
Transient nasal carriers
Persistent nasal noncarriers

* Total number of stud
† Transient: *S aureus* w

treatment regimen
persistence of 502A
teers who receive
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out of 17 (47%).
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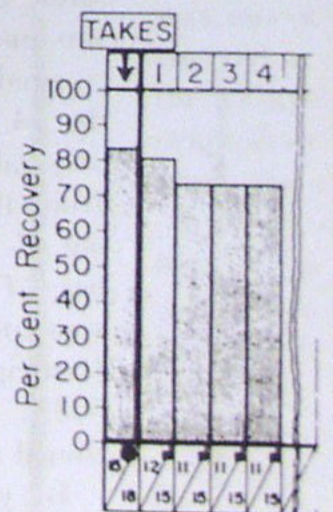


Fig 8.—Compar
cillin and 502A wi

TABLE 2.—*Staphylococcus Aureus* Carriage Among First Year Medical Students and First Year Nursing Students

	Medical Students (81 *)	Nursing Students (87 *)	Total
Persistent nasal carriers of coagulase-positive <i>S aureus</i>	30/81 (37%)	24/87 (28%)	54/168 (32%)
Transient † nasal carriers of coagulase-positive <i>S aureus</i>	21/81 (26%)	24/78 (28%)	45/168 (27%)
Persistent nasal noncarriers of coagulase positive <i>S aureus</i>	30/81 (37%)	39/87 (45%)	69/168 (41%)

* Total number of students cultured for four consecutive weeks.

† Transient: *S aureus* was not recovered from at least two of the four initial nasal cultures.

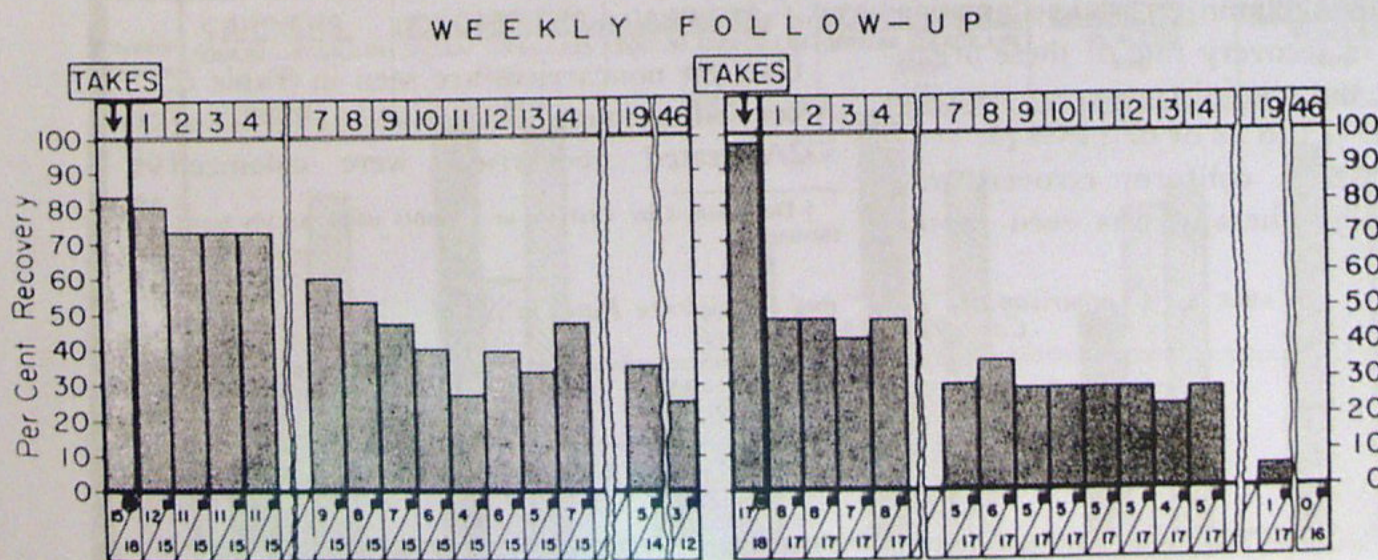
treatment regimens were stopped, the persistence of 502A was higher in the volunteers who received oxacillin before a 502A inoculation—11 out of 15 (73%) vs 8 out of 17 (47%). Striking differences were seen between the 502A inoculated oxacillin- and placebo-treated noncarriers at 19 and 46 weeks: five out of 14 (36%) and three out of 17 (25%) vs one out of 17 (6%) and zero out of 16 (0%).

Table 4 compares the aerobic nasal flora other than *S aureus* of carriers and noncarriers before any treatment regimen was instituted. Only *S aureus* and organisms grouped as micrococci, diphtheroids, and coliform types were included in the analysis since all other organisms found in the nasal flora were not recovered in sufficient numbers to be analyzed meaningfully. It is obvious that micrococci, diphtheroids, and coliforms were recovered more frequently in noncarriers than in carriers. From 188 cultures obtained from 38 carriers over a period of four weeks, micrococci, diphtheroids, and coliforms were isolated 91, 24,

and 41 times, respectively. From 221 cultures obtained from 45 noncarriers over a similar period of time, micrococci, diphtheroids, and coliforms were isolated 209, 88, and 83 times. Differences between carriers and noncarriers for each group of organisms was significant at $P = < 0.001$.

Fig 9 graphs the recovery rate* of micrococci before, during, and after treatment regimens for all oxacillin and placebo groups. Among carriers treated with sodium oxacillin, 53 of 115 (46%) of the cultures taken before treatment yielded micrococci (columns 1 and 3). During treatment the recovery rates of micrococci in carriers increased to 77 of 127 (61%). In the 14 weeks following cessation of oxacillin, cultures from carriers yielding micrococci increased even further to 181 of 240 (75%). As seen in column 5, during placebo administration, recovery rate of micrococci in carriers increased from a pretreatment rate of 38 of 73 (52%) to 60 of 79 (75%).

* Recovery rate is defined as the number of cultures yielding the particular organism in question per total cultures taken during the first 14 weeks of follow-up.



● Numbers of volunteers with 502A takes per numbers of volunteers inoculated.

■ Numbers of volunteers with persistence of 502A per numbers of available volunteers with takes.

Fig 8.—Comparison of acquisition and persistence of 502A in noncarriers treated with oxacillin and 502A with noncarriers treated with placebo and 502A.

Before oxacillin treatment, micrococci were recovered from 129 of 132 (98%) of the cultures taken from noncarriers (columns 2 and 4). During treatment this fell to 75 of 136 (55%), and after drug administration the number of cultures from which micrococci were recovered from noncarriers rose to 234 of 263 (89%). There was no observable change in the recovery rate of micrococci in the noncarrier group during or after administration of placebo capsules and nasal ointment (column 6).

The recovery rate of diphtheroids was reduced significantly among both carriers and noncarriers during treatment with sodium oxacillin (Fig 10, columns 1, 2, 3, and 4). Following cessation of antibiotic treatment diphtheroids reappeared to a small extent. However, for all oxacillin-treated groups, the follow-up recovery rate of diphtheroids was significantly lower than the pretreatment recovery rate. No significant change in the diphtheroid recovery rate during or after therapy was noted in the placebo-treated groups (columns 5 and 6).

Oxacillin had no consistent effect on recovery of coliform organisms from either carriers or noncarriers (Fig 11). In the group of carriers treated with sodium oxacillin (column 1) the recovery rate during oxacillin therapy fell from a pretreatment rate of 13 of 52 (25%) to 6 of 60 (10%); significant only at $P=0.05$. On the other hand, a second group of carriers treated with oxacillin (column 3) showed no significant fall in recovery rate of these organisms during the administration of oxacillin (17 of 63 [27%] to 12 of 67 [18%]).

An increase in coliform recovery rate during oxacillin therapy was seen in one

group of the noncarriers (column 2). It should be noted that the pre-oxacillin coliform recovery rate of 6 of 44 (14%) was considerably and inexplicably lower than a pretreatment recovery rate of 37 of 88 (42%) and 41 of 89 (46%) found in two other groups of noncarriers (columns 4 and 6).

The effect of *S aureus*, strain 502A, on the recolonization of carriers and noncarriers with various groups of organisms is summarized in Table 5 and 6. After sodium oxacillin and 502A therapy, the recovery rate of *S aureus* other than 502A among carriers challenged with 502A during the first 14 weeks of the follow-up was 31 of 130 (24%) while the recovery rate in individuals who were simply challenged with saline was 53 of 110 (48%); significant at $P < 0.01$ (Table 5).

During the 14 weeks after antibiotics were stopped, carriers treated with either saline or 502A showed an increase in the recovery rate of micrococci from the nasal mucosa. The recovery rate in the 502A-treated volunteers increased from 36 of 67 (54%) during treatment to 90 of 130 (69%) while in the saline-treated individuals the change in the recovery rate was from 41 of 60 (68%) to 91 of 110 (83%). The difference in increase between these groups was not significant ($P = > 0.2$).[†] After oxacillin, changes in recovery rates of diphtheroids and coliforms were small and were similar in 502A and saline-treated students.

Data on noncarriers are seen in Table 6. After sodium oxacillin nine of 162 (5%) of 502A-treated noncarriers were colonized

[†] Determined by analysis of variants using arcsin transformation.

TABLE 3.—Comparison of "Take" and Persistence Rates in Nasal Carriers and Noncarriers

Subject	"Take" Rates (%)	Persistence Rate		
		4 Wk	19 Wk	46 Wk
Group 3 carriers: treated with sodium oxacillin and challenged with 502A	13/13 (100)	11/13 (85)	4/11 (36)	2/10 (20)
Group 5 carriers: treated with placebo and challenged with 502A	9/14 (64)	2/9 (22)	0/9 (0)	0/9 (0)
Group 4 noncarriers: treated with sodium oxacillin and challenged with 502A	15/18 (83)	11/15 (73)	5/14 (36)	3/12 (25)
Group 6 noncarriers: treated with placebo and challenged with 502A	17/18 (94)	8/17 (47)	1/17 (6)	0/16 (0)

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* Number of culture period before antibiotic
† Differences between

with *S aureus* recovery rate in saline was 15% of micrococci carriers went from oxacillin therapy while organism in 1 from 28 of 45 $P = > 0.2$. C during the pe administered, 50 carriers both diphtheroids while coliform groups were e

Results from carriers and strain 502A

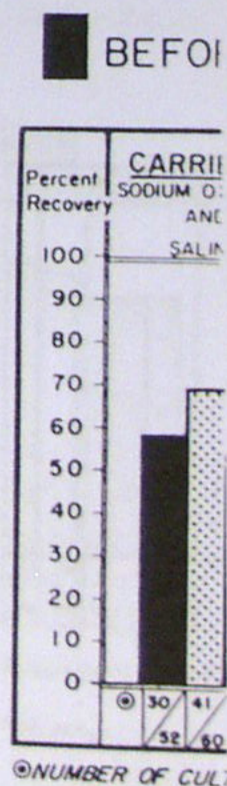


Fig 9.—Pe

TABLE 4.—Normal Nasal Flora of Persistent Carriers and Persistent Noncarriers of *Staphylococcus aureus*

Organism	Carriers * (%)	Noncarriers * (%)
Micrococci	91/188 (48) †	209/221 (95) †
Diphtheroids	24/188 (13) †	88/221 (40) †
Coliforms	41/188 (22) †	83/221 (38) †

* Number of cultures yielding particular organism per total cultures taken on all members in the study (83) during the four-week period before antibiotics.

† Differences between carrier and noncarrier significant for each group of organisms at $P = <0.001$.

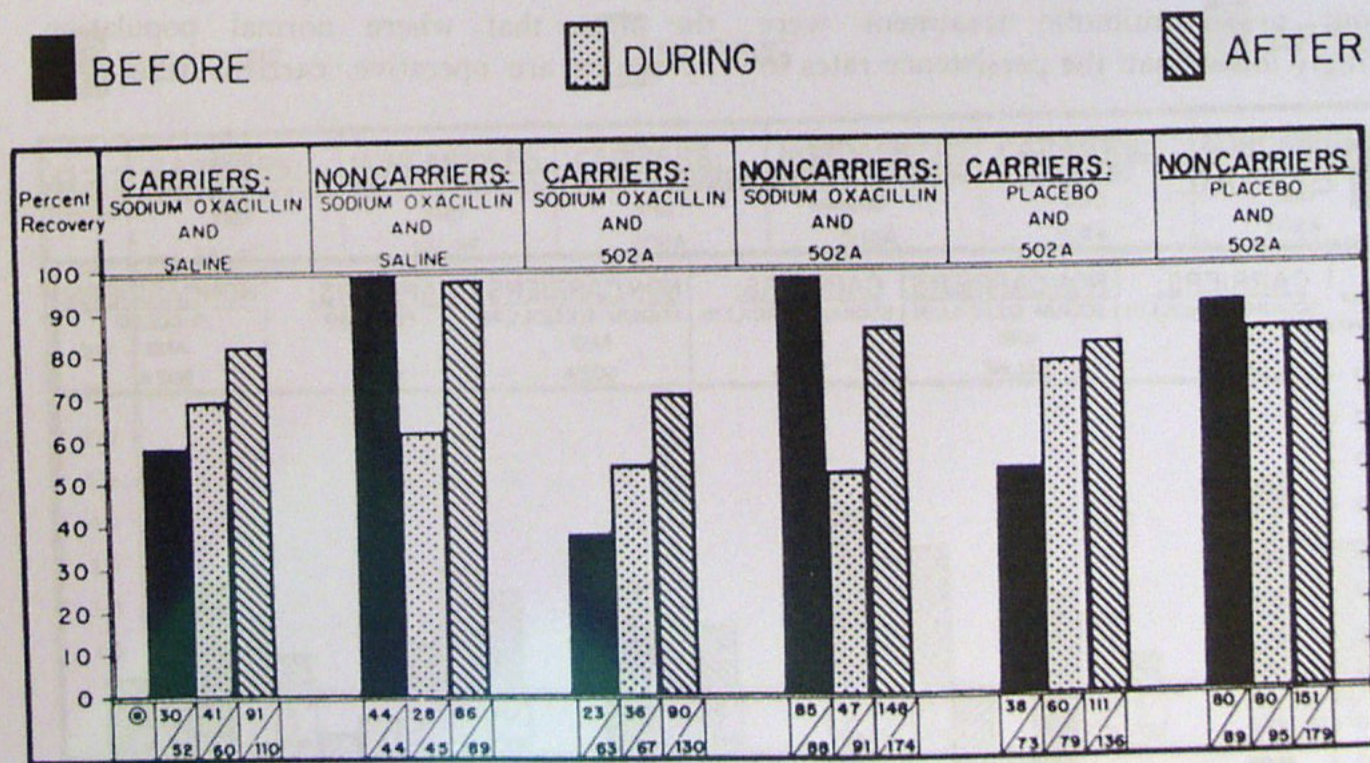
with *S aureus* other than 502A while the recovery rate in noncarriers challenged with saline was 15% (12 of 81). Recovery rate of micrococci in the 502A-treated noncarriers went from 47 of 91 (52%) during oxacillin therapy to 148 of 174 (85%) after therapy while the recovery rate of this organism in the saline-treated group went from 28 of 45 (62%) to 86 of 89 (97%) $P = >0.2$. Compared to recovery rates during the period when oxacillin was administered, 502A- and saline-treated noncarriers both showed an increase of diphtheroids during the follow-up period while coliform recovery rates in both these groups were essentially unchanged.

Comment

Results from challenging staphylococcal carriers and noncarriers with *S aureus* strain 502A (Table 3) showed that non-

carriers acquired and retained the inoculated strain more easily than carriers. Heavy colonization with resident strains of *S aureus* inhibited nasal colonization with 502A. This is similar to our data obtained from volunteers at the Federal Penitentiary which also demonstrated that heavy colonization with resident strains of *S aureus* interfered with subsequent colonization by challenge staphylococcal strains.⁷

However, if carriers are given oxacillin before 502A is inoculated, the nasal mucosa is susceptible to colonization. The carriage rate in this group of students at ten weeks after inoculation was 47%: considerably less than the ten-week persistence rate of 92% observed in the penitentiary volunteers.⁷ Multiple factors operative in a hospital environment that tend to reduce the nasal carriage rate of penicillin-sensitive *S aureus* probably account for this difference.



©NUMBER OF CULTURES YIELDING ORGANISM PER TOTAL CULTURES TAKEN.

Fig 9.—Percent of cultures yielding micrococci before, during, and after treatment regimens.

TABLE 5.—Nasal Flora Recovered From *S aureus* Nasal Carriers Before and After Treatment With Sodium Oxacillin and 502A or Sodium Oxacillin and Saline

Organism	Sodium Oxacillin and 502A			Sodium Oxacillin and Saline		
	Before (%)	During (%)	After (%) *	Before (%)	During (%)	After (%) *
<i>S. aureus</i> other than 502A	—	—	31/130 (24)	—	—	53/110 (48)
Micrococci †	23/63 (37)	36/67 (54)	90/130 (69)	30/52 (58)	41/60 (68)	91/110 (83)
Diphtheroids †	8/63 (13)	0/67 (0)	1/130 (1)	7/52 (14)	1/60 (2)	4/110 (4)
Coliforms †	17/63 (27)	12/67 (18)	19/130 (15)	13/52 (25)	6/60 (10)	9/110 (8)

* Number of cultures yielding particular organism/total cultures taken during 14-week follow-up (per cent).
 † Recovery rate during and after oxacillin and 502A compared to recovery rate during and after oxacillin and saline not significantly different ($P = >0.2$ determined by analysis of variants using arsenic transformation).

It must be emphasized that "heavy colonization" is an important qualification of the nasal colonization status when evaluating data on staphylococcal interference. Recent data demonstrated that the protection against artificial colonization of individuals who carry relatively few colonies of *S aureus* on their nasal mucosa was considerably less than of heavily colonized volunteers.⁸ All the carriers in this study as well as those in the concurrent study⁷ were "heavily colonized".

The present data also suggest that there are other inhibitory factors aside from the *S aureus* that influence nasal colonization with deliberately inoculated 502A. For example, at the 19-week follow-up, persistence rates in the noncarriers challenged with 502A without prior antibiotic treatment were strikingly lower than the persistence rates in

noncarriers treated with sodium oxacillin and then inoculated with 502A (6% vs 36% respectively). Treatment of noncarriers with sodium oxacillin raised persistence rates to essentially those rates observed in carriers who were pretreated with sodium oxacillin before they were inoculated. This suggested that any difference in noncarriers and carriers could be ablated by systemic and local treatment with sodium oxacillin.

Whether antibiotics render both carriers and noncarriers equally susceptible to staphylococcal colonization when exposed to staphylococci not by direct inoculation but under normal living conditions is a question that has not been answered in the present study. There is, however, a suggestion in the data that where normal population dynamics are operative, carriers who have

TAI
 Organism
S. aureus other than Micrococci †
 Diphtheroids †
 Coliforms †
 * Number of cultures
 † Recovery rate different ($P = >0.2$)

been treated susceptible to mental strain who had identified. During the first four of 11 individuals acquired a strain carried it twice phenomenon nine in the list.

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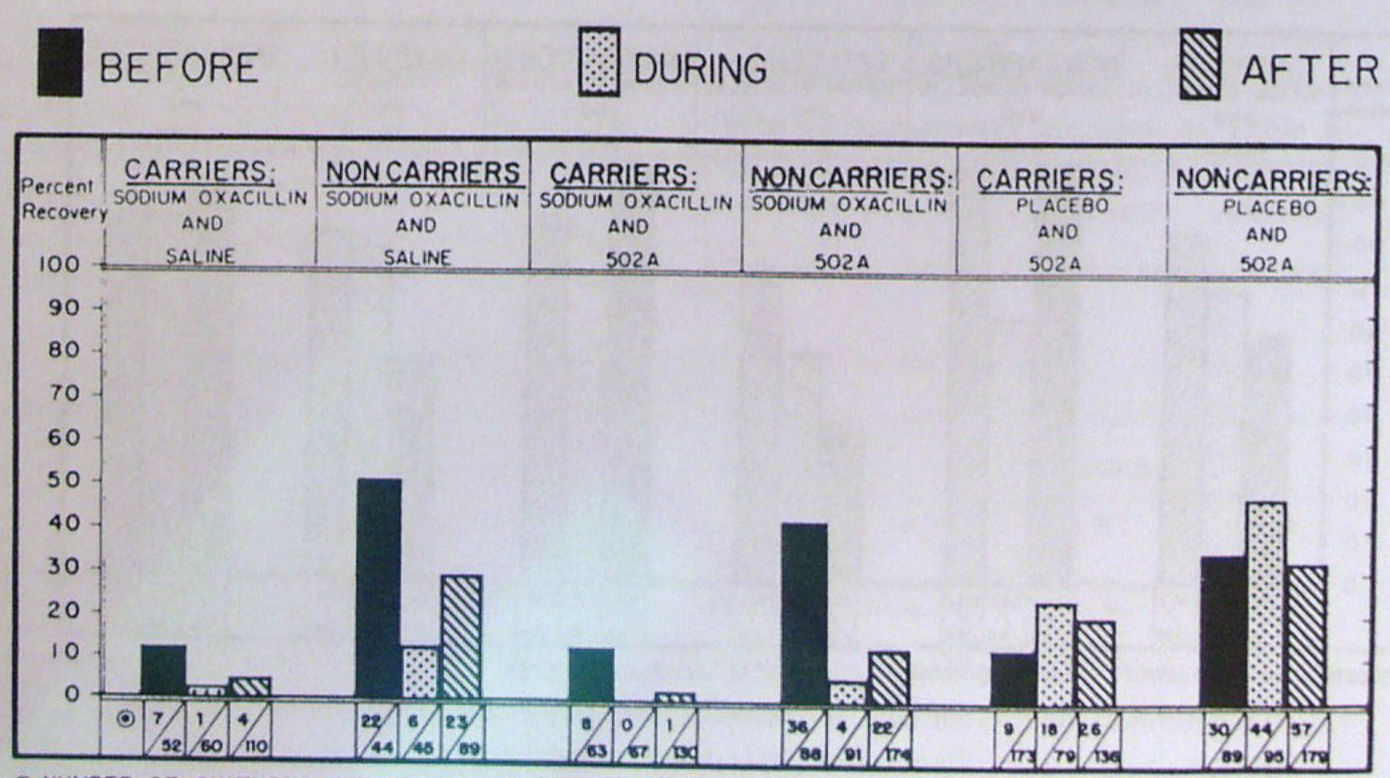


Fig 10.—Percent of cultures yielding diphtheroids before, during, and after treatment regimens. Amer J Dis Child—Vol 111, Jan 1966

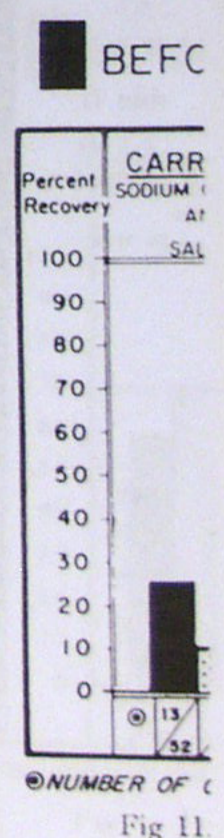


Fig 11.

TABLE 6.—Nasal Flora Recovered From Noncarriers Before and After Treatment With Sodium Oxacillin and 502A or Sodium Oxacillin and Saline

Organism	Sodium Oxacillin and 502A			Sodium Oxacillin and Saline		
	Before (%)	During (%)	After (%) *	Before (%)	During (%)	After (%) *
<i>S. aureus</i> other than 502A	—	—	9/162 (6)	—	—	12/81 (15)
Micrococci †	85/188 (97)	47/91 (52)	148/174 (85)	44/44 (100)	28/45 (62)	86/89 (97)
Diphtheroids †	36/88 (41)	4/91 (4)	22/174 (13)	22/44 (50)	6/45 (13)	23/89 (26)
Coliforms †	37/88 (42)	27/91 (30)	55/174 (32)	5/44 (11)	13/45 (29)	21/89 (24)

* Number of cultures yielding particular organism/total cultures taken during 14-week follow-up (per cent).
 † Recovery rate during and after oxacillin and 502A compared to recovery rate during and after oxacillin and saline not significantly different ($P = >0.2$ determined by analysis of variants using aresin transformation).

been treated with oxacillin will be more susceptible to colonization with environmental strains of *S aureus* than noncarriers who had identical treatment (Fig 1 and 2). During the first 19-week follow-up period four of 11 individuals in the former group acquired a new strain of *S aureus* and carried it two weeks or longer, while this phenomenon was observed in only one of nine in the latter group.

The factors responsible for this phenomenon of bacterial interference are not known. Two experimental models in animals are being studied in an attempt to understand the mechanism(s) involved in this type of protection. Ribble and Shinefield demonstrated staphylococcal interference in the allantoic cavity of fertile chick eggs¹⁰ while Anthony and Wannamaker have observed the same phenomenon at burn sites of rabbit skin.¹¹

In addition, Ribble has obtained experimental evidence which suggests that staphylococci grown in vitro produce a substance which interferes with utilization of nicotinamide by staphylococci.¹² How, if at all, this substance is involved in staphylococcal interference in vivo is speculative at the moment.

The relationship of *S aureus* to the other organisms that comprise the normal biota of the nasal mucosa is of considerable interest. Factors involved in maintaining a balance between the biota of the nasal mucosa are not well defined, but the present data support the observation of others that *S aureus* carriers are not as likely as noncarriers to be colonized with a variety of organisms other than *S aureus* considered to be normal components of the nasal flora.¹³

In the present study the effect of oxacillin

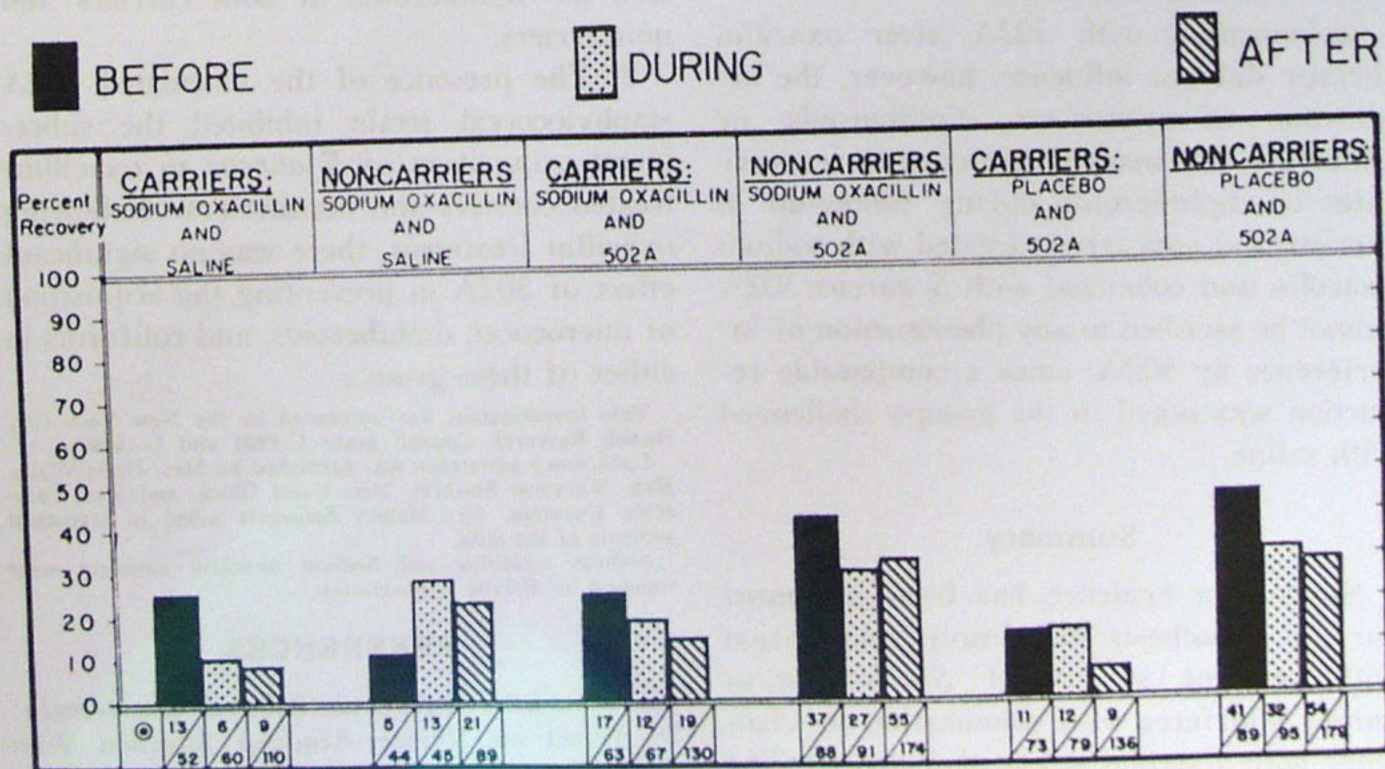


Fig 11.—Percent of cultures yielding coliforms before, during, and after treatment regimens.

on groups of organisms other than *S aureus* depended on the host as well as the type of organism encountered. For example, oxacillin treatment markedly reduced the recovery rate of micrococci in noncarriers whereas the recovery rate of micrococci from carriers increased during the administration of oxacillin. The meaning of this increase is not clear since an increase in the recovery rate of micrococci was also seen in the placebo-treated carriers. On the other hand oxacillin virtually eliminated diphtheroids from both carriers and noncarriers while in both these groups little effect of oxacillin on the recovery rate of coliforms was noted.

The data also demonstrated the selective protective effect of deliberate nasal colonization with strain 502A. Comparison of recovery rates of other strains of *S aureus* during a 14-week follow-up period between carriers and noncarriers treated with sodium oxacillin and challenged with saline, and carriers and noncarriers also treated with sodium oxacillin but challenged with 502A, showed that once the inoculated strain heavily colonized volunteers, it interfered with subsequent spontaneous colonization by other strains of *S aureus*.

Colonization with 502A after oxacillin therapy did not influence, however, the acquisition of micrococci, diphtheroids, or coliforms. The marked reduction in recovery rates of diphtheroids during follow-up in carriers and noncarriers treated with sodium oxacillin and colonized with *S aureus* 502A cannot be ascribed to any phenomenon of interference by 502A, since a comparable reduction was noted in the groups challenged with saline.

Summary

Supporting evidence has been presented for the hypothesis that heavy colonization with resident strains of *Staphylococcus aureus* interferes with colonization by challenge with a second strain of *S aureus*. The data clearly demonstrated that the presence of one strain of *S aureus* on the nasal mucosa makes it difficult if not impossible for a second *S aureus* strain to colonize this site.

Noncarriers acquired and persistently carried the challenge strain more easily than carriers. One week after inoculation the implanted 502A strain was carried by 53% of the untreated noncarriers but by only 21% of the untreated carriers. This striking difference was noted throughout the entire 46-week follow-up period.

The data also suggest that other factors may interfere with deliberate attempts to colonize the nasal mucosa, but that these factors as well as the inhibitory effect of resident strains of *S aureus* can be suppressed or eliminated with systemic and local oxacillin treatment.

In fact, after antibiotic treatment, 502A take and persistence rates were the same in carriers and noncarriers.

Information gained in the present study on organisms other than *S aureus* found on the nasal mucosa may be summarized as follows:

1. *S aureus* carriers are not as likely as noncarriers to be colonized with micrococci, diphtheroids, or coliform groups of organisms.
2. Oxacillin was effective in eliminating or suppressing micrococci in noncarriers as well as diphtheroids in both carriers and noncarriers.
3. The presence of the inoculated 502A staphylococcal strain inhibited the subsequent acquisition of *S aureus* in oxacillin-treated carriers and noncarriers. Following oxacillin treatment, there was no significant effect of 502A in preventing the acquisition of micrococci, diphtheroids, and coliforms in either of these groups.

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