Bacterial Interference Treatment of Recurrent Furunculosis

2. Demonstration of the Relationship of Strain to Pathogenicity

Walter G. Strauss, MD; Howard I. Maibach, MD; and Henry R. Shinefield, MD

Three patients with furunculosis due to a pathogenic strain of *Staphylococcus aureus* became free of furuncles after *S aureus* strain 502A was purposely substituted. Relapse of furunculosis occurred when 502A was lost and the original strain reacquired. Nine other patients lost their furuncles after replacement of a pathogenic strain by 502A. Abscess formation is a strain-related phenomenon in these patients, and disappearance of furuncles was not a chance event but was related to the implantation of strain 502A.

THE PRINCIPLE of bacterial interference has been applied successfully to the interruption of staphylococcal epidemics in nurseries. We have utilized a similar principle to interrupt recurrent staphylococcal furunculosis in individual patients.[1] With administration of systemic antibiotics the patient's pathogenic staphylococcal carriage can be greatly diminished or eliminated. After cessation of antibiotic therapy, recolonization can be manipulated by seeding the nose and skin with staphylococcal strains, such as strain 502A, chosen for their decreased virulence.

Our first patient with furunculosis was purposefully colonized with *Staphylococcus aureus*, strain 502A, five years ago. She has carried this strain on her skin and has remained free of furuncles. However convincing this clinical demonstration might be, the possibility existed that the bacterial transplantation and loss of furuncles were coincidental and not causally related. While we were planning a controlled trial, three patients who were previously given transplants with stain 502A had relapses of furuncles. This permitted observations which demonstrated that absence or presence of furuncles is indeed a phenomenon related to *Staphylococcus* strain.

Methods and Materials

Patients were selected for purposeful colonization with strain 502A if furuncles containing *S aureus*, coagulase-positive, had been present for a minimum of one year. During a period when the patient was temporarily free of furuncles, oxacillin sodium tablets (250 mg) were given four times a day for 14 days. On the 15th day *S aureus*, coagulase-positive, strain 502A, was first implanted. Implanting fluid consisted of a 24-hour broth culture containing 10^9 live organisms per milliliter. Single drops were placed on the surface of the skin of the axillae, umbilicus, groin regions, perineum, and popliteal fossae and in each naris daily for five days.

Cultures of the colonized sites plus cultures of the throat and anus were done before treatment, after implantation, and intermittently for a period of one to three years. A sterile saline-moistened alginate sodium applicator was swabbed across the site and streaked onto a tellurite plate. Five colonies were picked for phage typing.

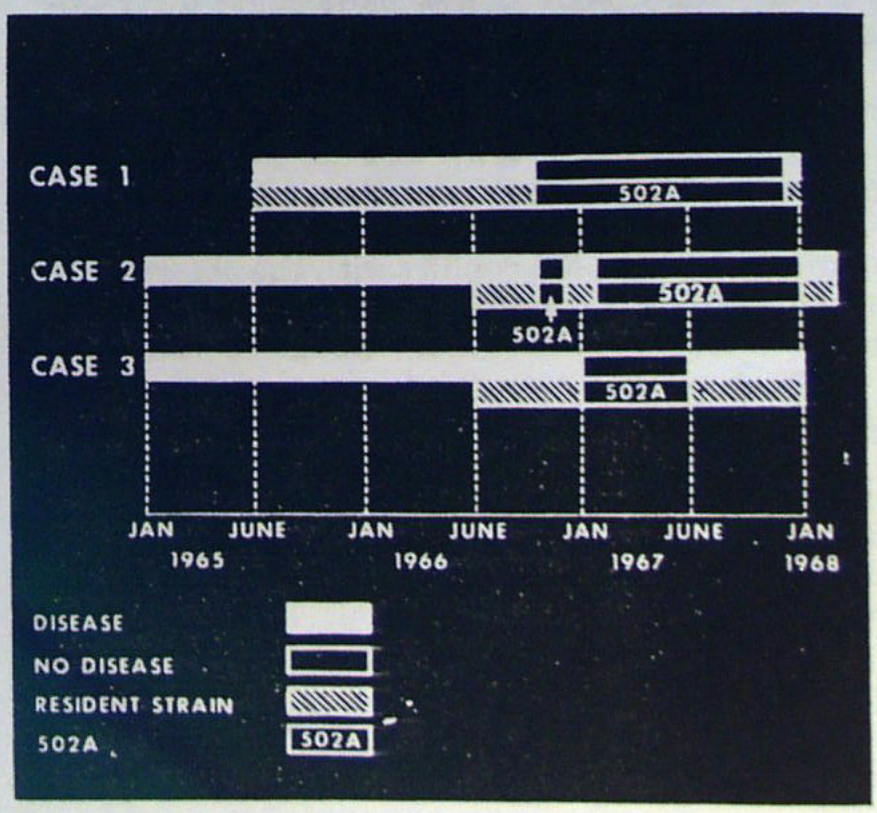
Strain 502A is usually phage type 6/7/42D/44A/53/54/75/81. It is sensitive to penicillin and high doses of tetracycline hydrochloride, and resistant to low doses of tetracycline.

Report of Cases

CASE 1.—A 20-year-old girl had multiple furuncles between June 1965 and September 1966. Culture of pus from furuncles and her nose grew *S aureus*, phage type 3B/55/71. Cultures of other sites did not yield *S aureus*. She received oxacillin and was colonized with strain 502A in September 1966. Strain 502A was cultured from multiple sites in October, November, and December 1966 and January 1967. All sites were negative for coagulase-positive staphylococci in June 1967. In December 1967, she had the first recurrent furuncle since 502A transplantation. Cultures of her nose and the lesions revealed her original strain (phage type 3B/55/71), but no strain 502A. Thus she had two periods of furunculosis with a pathogenic strain separated by another period of several months' duration during which she was free of furuncles and carried strain 502A or no *S aureus*.

CASE 2.—A 46-year-old man had many furuncles from 1962 to 1966 due to *S aureus*, phage type 52A/79. He received oxacillin and was colonized with strain 502A in October 1966; he carried only that strain for one month. During this month he had no lesions, but in November he had a furuncle due to type 52A/79. He was recolonized with 502A in January 1967. Throughout 1967 he carried only 502A and had no lesions. In January 1968, 52A/79 was cultured from his skin and shortly afterwards he be-

Staphylococcal disease related to nasal colonization with *Staphylococcus aureus*, type 502A.



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gan having abscesses again. These all contained phage type 52A/79. This patient then had two periods of furunculosis due to 52A/79 and two periods free of furuncles during which he carried strain 502A.

CASE 3.—A 10-year-old boy had numerous furuncles from 1962 to 1966. Phage type 52A/79+ was repeatedly cultured from the furuncles and from clinically uninvolved skin. He received oxacillin, was colonized with strain 502A in January 1967, and carried this strain for six months during which time he was asymptomatic. Then he had a sty from which type 52A/79+ was cultured. Cultures of the nose and throat were positive for 52A/79+ but no 502A was recovered. He had a furuncle of the upper lip in September 1967 from which 52A/79+ was cultured. Again, this patient had two episodes of furunculosis with his usual strain separated by a period free of furuncles during which time he carried only strain 502A.

Comment

A common phenomenon occurred in the three patients (Figure). Furuncles were associated only with carriage of the patient's original strain of *Staphylococcus*. During periods of 502A carriage, these patients were free of lesions. The sequence consisted of the presence of furuncles associated with the original strain, freedom from lesions while the patient carried strain 502A, and then relapse when 502A was lost and replaced by the original pathogenic strain. This sequence provided the necessary evidence to establish that strain 502A is less pathogenic for these hosts and that it can interrupt furunculosis.

In addition, we have transplanted strain 502A onto 11 patients and have followed up these patients for at least one year. Of these 11, nine have retained strain 502A and have had no furuncles. One patient, on whom strain 502A was successfully transplanted, ceased having furuncles and then had a recurrence of his previous strain, but new furuncles have not developed so far. We have also followed up one patient whose colonization was unsuccessful, and who retained the original strain but spontaneously lost his furuncles. These observations provide additional support to the hypothesis that strain 502A is less pathogenic for these patients with recurrent furunculosis.

This and the experience of Boris et al,[2] who have only rarely seen furuncles in patient who carried only strain 502A, has convinced us that furuncles are indeed strain-related, and that 502A has only a minimal proclivity to produce furuncles. This interpretation does not conflict with the observation that abscesses may disappear from a patient who retains or regains the original pathogenic strain.

Two observations require additional comment. In our experience, strain 502A may produce pustules at the time and site of colonization. These are never larger than 2 mm and are seen particularly on glabrous skin. We have not observed them after the implantation procedure is finished, despite the persistence of 502A. Boris et al[2] have observed three small lesions (two pustules and one sty) in patients transplanted with 502A.

Finally, strain 502A has been cultured from four large abscesses in a patient observed by Drutz et al.[3] In two of these abscesses the original pathogenic strain was present as well as strain 502A; in two other abscesses only 502A was present. This and other data[2] demonstrate that on rare occasions strain 502A can be associated with disease. However, in the case reported by Drutz et al it should be noted the patient had a skin disease and was using topical application of steroids. Both these host factors may have been important in increasing susceptibility to disease in this patient. A two-year follow-up of this patient after nasal colonization with strain 502A is significant in that she experienced no further staphylococcal disease of any type, other than the lesions noted in the published communication[3] according to an oral communication from M. G. Koenig, MD, in November 1968.

This investigation was supported in part by grant NGR-05-025-008 from the National Aeronautics and Space Administration and by contract DA-49-193-MD-2466 from the US Army Medical Research and Development Command, Department of the Army.

Technical assistance was provided by Sally Ronquillo and Kitty Phelps.

Generic and Trade Names of Drugs

Oxacillin sodium—*Prostaphlin, Resistopen.*
Tetracycline hydrochloride—*Achromycin V, Bristacycline, Panmycin Hydrochloride, Steclin, Tetracyn Hydrochloride.*

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STRATFORD HOSPITAL

TELEPHONES:
MAIN HOSPITAL - 7189
MATERNITY ANNEXE 7078
SECRETARY - - 6018

YOUR REF. _____
OUR REF. _____

Miranda Street,
Stratford,
TARANAKI, N.Z.

11th May 1970.

Dr H.R. Shinefield,
Department of Pediatrics,
The Permanente Medical Group,
2200 O'Farrell St,
San Francisco,
CALIFORNIA. 94115

Dear Dr Shinefield,

Dr H.T. Knights of the National Health Institute forwarded to me the proforma for your 502A survey. I am returning this to you with apologies for the delay, but felt it would be of greater value to you to have an up-to-date culture report; so have waited for this to be completed. It seemed more convenient to set out the answers to question 10 - 17 in the form of a table on separate sheet.

I am glad of this apportunity of thanking you for your co-operation in providing the organisms. Prior to your treatment this patient was a spotty unhealthy unhappy girl who would undoubtedly have been forced to give up her nursing career on account of recurrent sickness and permanent carrier state; since treatment she has blossomed into a healthy happy girl who has completed her training and is now a valued member of our registered nursing staff, and has quite recently got married.

This case is a great tribute to your method of treatment. I enclose a copy of our article from the New Zealand Medical Journal which includes the case report on this patient.

With regards,

Yours sincerely,

Carey C.K. Smith

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CAREY C.K. SMITH F.R.C.S.
MEDICAL SUPERINTENDENT

7/8/70

S.S.

N.Z. med. J., 67, 407. (March 1968)

both complement.
Cars Ch Smith

Bacterial Substitution for Staphylococcal Infection

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SUMMARY

A case is presented of a persistent pathogenic staphylococcal carrier state, resistant to all conventional therapy, causing recurrent episodes of furunculosis, and threatening to terminate the patient's nursing career. A new therapeutic technique utilising the principle of "bacterial interference" is described. The pathogenic resident organism was removed by the administration of antibiotics, and a relatively avirulent strain of staphylococcus was substituted by artificial colonisation. A year followed with only one transient infection, and the patient was able to complete her nursing training. The avirulent strain was still present one year after colonisation.

Earlier work is summarised, and the benefits and dangers of this technique are discussed. The principle of "bacterial interference" has possible application in the prevention of maternity hospital staphylococcal outbreaks and in the treatment of staphylococcal carriers and individuals susceptible to infection.

INTRODUCTION

Individuals harbouring virulent staphylococci or plagued by recurrent skin infections, continue to present a problem, particularly in hospitals, despite modern antibiotics, autogenous vaccines, and methods to control spread.

Shinefield and others (1963) have introduced a new approach to this problem by artificially colonising infants soon after birth with a non-virulent strain of staphylococcus (designated 502A) during nursery outbreaks of infection with staphylococcus aureus phage type 80/81. Strain 502A became established on the infants, and prevented colonisation by the virulent strain.

This method of "bacterial interference" has also been attempted successfully in adults. Artificial colonisation trials amongst prisoners (Boris and others, 1964), and medical and nursing students (Shinefield and others, 1966), following therapy with oxacillin to remove the resident strain, resulted in colonisation with 502A for up to twenty weeks in previous carriers of virulent strains. Strauss, Marbach and Hurst (1965) have successfully colonised a patient with severe recurrent furunculosis. There was no further infection in 13 months, and 502A continued to be isolated from the patient and several contacts. Success in a whole family with recurrent staphylococcal infections has been reported by Fine and others (1967).

This paper details a similar attempt in a nurse whose training was threatened by persistent staphylococcal infection.

CASE REPORT

Miss J. G., aged 22, started her nursing career five and a-half years before this trial. For the last two and a-half years she had been troubled by recurrent crops of superficial staphylococcal infections, involving skin, eyes, and nose, and several times she required hospital admission with consequent interruptions to her training. During one break of over a year's duration she took an outdoor job in an attempt to free herself of infection. She was found to be a nasal and skin carrier of staphylococcus aureus phage type 52/52A/80/81, and persistent attempts to remove this organism with a variety of antibiotics, autogenous staphylococcal vaccines, and local applications, were all unsuccessful.

Since commencing her nursing training, she had suffered recurrent attacks of bronchial asthma, and also eczema for which she had received local steroid preparations on occasion. No other significant history was obtained, and there were no known staphylococcal carriers among her contacts.

In 1966 after 2½ years of these infections it became apparent that unless a method could be found to rid her of pathogenic staphylococci, the risk to patients particularly in the maternity and surgical fields would prevent her completing her nursing training. It was therefore decided to attempt artificial colonisation.

METHOD

A month's course of oral ampicillin 250mg four times daily in June and July 1966, failed to rid her nostrils of the staphylococcus for any length of time; but following this course and the use successively of neomycin with chlorhexidine, nitrofurazone, and chloromycetin applied locally into the nares, in September 1966 a negative swab was at last obtained from the nostrils. Recolonisation was immediately commenced using a variation of the method described by Strauss and others (1965).

On admission to hospital medication was stopped. Lyophilised staphylococcus aureus strain 502A, obtained from Dr Shinefield through the National Health Institute, Wellington, was reconstituted by adding 1cc of sterile distilled water, and incubating this in trypticase soy broth. After about 18 hours of growth, the patient was inoculated by placing one drop of the culture in each nostril, each axilla, the umbilicus, groin and perianal areas, on nine successive days.

RESULTS

Shinefield's strain 502A was isolated consistently from multiple skin sites, along with coagulase negative staphylococci, for three months, and no further infections occurred. The patient was able to return to her nursing. Six months after colonisation she developed an inflammation of her anterior nares, and staphylococcus phage type 52/52A/80/81 was isolated.

The infection cleared within a week with oral erythromycin, and two weeks later a variant of Shinefield's strain was again isolated from the nose. One year after initial colonisation no further infections had developed, and strain 502A was still resident in both nostrils.

DISCUSSION

The case presented is the first known trial in New Zealand (Knights, 1967) of a method of treating staphylococcal carriers in some ways analagous to the introduction of lactobacillus into the human intestine to prevent multiplication of unwanted organisms. Unfortunately, due to host factors not yet elucidated, some individuals seem fated to harbour a staphylococcus, and a relatively avirulent organism would appear to be preferable to a virulent strain in individuals in contact with infants and patients, or susceptible to infection themselves.

The strain designated 502A has caused mild superficial pustules in a small proportion of cases, and in one study (Drutz and others, 1966) was isolated from overt abscesses in a patient with an underlying chronic skin disorder. However, in general Shinefield's strain has relatively low virulence compared with a strain such as 52/52A/80/81, and seems to be an ideal organism for use in artificial colonisation (Eichenwald, Shinefield, Boris, and Ribble, 1965).

In our patient a significant feature was the development of an infection by a virulent strain after colonisation by 502A. The 502A appeared again after an antibiotic course had disposed of the infection, and it would seem that the 502A had sufficient hold to withstand erythromycin, or alternatively was on the mucous membrane out of reach of the systemic antibiotic, in which case it might have succumbed to a local application.

In contrast to earlier trials, our patient was not free of staphylococcus for an appreciable period prior to artificial colonisation. However it was decided to proceed, since there was no danger to the patient in a failed attempt, and further attempts could have been made at a later date if necessary. The first attempt at colonisation was, in fact, successful.

A variation in phage typing of the avirulent resident strain has been evident. The original 502A was reported to lyse phages 7/47/53/81 (Eichenwald and others, 1965), and the National Health Institute have typed the original organism as 7/53/83A+, using 1,000 RTD. Following substitution, successive cultures obtained from the patient have typed as follows:

53/83A+	53/81+
42E/53/83A+	42E/53/77/42D
6/53/81+	42E/47/53+/81

It is probable that these are all variants of the original strain 502A.

We have applied to this technique the term "bacterial substitution", which seems preferable to "bacterial interference" used in earlier work. The latter term could perhaps be retained to describe the phenomenon by which one resident organism prevents colonisation by another strain, a concept as yet poorly understood. Theories include the production by the resident organism of a substance, termed a colicin (Light and others, 1965), analogous to interferon produced by viruses; and Ribble (1965) considers that the interference is in some way related to nicotinamide utilisation.

Whatever the mechanism, we feel that this new concept is a significant advance in the treatment and prevention of staphylococcal infection; and that it could be of benefit not only in resistant staphylococcal carriers such as this case, but also in averting maternity hospital outbreaks of staphylococcal infection, as achieved by Shinefield and others (1963).

ACKNOWLEDGMENTS

We are grateful to Dr H. T. Knights for supplying us with the Shinefield 502A strain, and for his advice and help throughout this trial.

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502A SURVEY *

1. Name of Patient Mrs JEAN PERRETT (NÉE GOLDUP) 2. Age 22 3. Sex F

4. Address STRATFORD HOSPITAL 5. Telephone # STRATFORD N2. 7721

6. Complaint RECURRENT FURUNCULOSIS
NASAL AND SKIN CARRIER of STAPH 52/52A/80/81 7. Duration 2½ years

8. Previous Rx Variety of antibiotics & autogenous vaccines 9. Lesions cultured: Yes ✓ No ____

10. If cultured:

DATE	RESULT	Penicillin SENS.	Penicillin RES.	PHAGE TYPE

11. Cultures before antibiotic + 502A therapy

DATE	SITE	RESULT	Penicillin SENS.	Penicillin RES.	PHAGE TYPE

12. Antibiotic therapy:

Local
Nasal Yes____ No____ Type_____ Duration_____

Other Yes____ No____ Type_____ Duration_____

Systemic Yes____ No____ Type_____ Duration_____

13. Culture just before 502A colonization

DATE	SITE	RESULT	Penicillin SENS.	Penicillin RES.	PHAGE TYPE

See separate sheet

14. 502A inoculation DATE SEPT 1966 SITE Nostrils, Axillae, Groins, Perianal, Umbilicus

15. Length of follow up after 502A Years 3 Months 7 Days ____

See separate sheet

16. Cultures after 502A inoculation (include lesions)

DATE	SITE	RESULT	Penicillin SENS	Penicillin RES	PHAGE TYPE

17. Comments: (If patient treated for recurrent furunculosis please state frequency of lesions before and after 502A colonization)

Approximately every month for 3 years preceding Colonisation. Two lesions in three and a half years following Colonisation.

18. Any underlying disease Yes ✓ No ____

Type Bronchial Asthma; this has also considerably improved since inoculation with Shinefield 502A.

* Please fill a separate survey out for each patient or family member that has been treated and indicate under complaint that the patient is being treated not because of disease but because he is a family member of a patient with disease.

MRS JEAN PERRETT (NEE' GOLDUP) STRATFORD HOSPITAL. N.Z.

SURVEY OF LESIONS, CULTURES AND TREATMENT.

Date	Site of Purulent Lesion.	Swab taken.	Organsims.	Penicillin Sensitivity	TREATMENT Local Preparation	Oral or Systemic Antibiotics	Other.
1963 Dec 3	Skin	Pus	Staph aureus (Not typed)	S	-	-	-
1964 Jan 27	"	"	" " "	S	-	-	-
May 16	"	"	" " "	S	-	-	-
June 4	Nose	Nose	" " "	S	Framycin	-	-
June 27	Eye	"	Staph phage type 52/52A/80/81	R	Framycin	Chloromyctein	Hospitalisation 3 days.
Aug							Autogenous Vaccine
Sept) Oct)	Eye	Pus	" " " "		Neomycin) Polymycin) Bacitiacin)	Tetracycline	Hospital 1 week. Autogenous Vaccine
					Chloromycetin Erythromycin		Hospital 4 days.
Dec	Eye	Pus	" " " "	R	Chloromycetin	Chloromycetin	
		Nose	" " " "	R		Phenethicillin	Sick leave
1965 Jan		Nose	Staph aureus (not typed)	R			
Mar		Nose	" " "	R			
Apr	Skin	Pus	" " "	R			
June	Nose				Gramacidin	Spiramycin	
July	Skin	Pus	" " "	R		Erythromycin	Hospital 3 days.
Sept				R			
Oct		Nose	" " "	R			
Nov	Skin						
Dec	Skin						

Extended leave from Nursing for One Year

Date	Site of Purulent Lesion.	Swab taken.	Organism.	Penicillin Sensitivity	Local Preparation	Oral or Systemic Antibiotics	Other
1966 Jan	Skin						
1966 Mar	Eye	Pus	Staph aureus (Not typed)	R			
April	Eye						
June	Skin	Pus, Skin, nose	Staph 52/52A/80/81	R			
	Skin	Pus	Staph aureus (Not typed)		Neomycin Antiseptics	Ampicillin	Hospital 4 days
July	Skin				Nitrofurazone		Hospital 1 week.
Aug	Skin	Nose	" " " "		Chloromycetin		Hospital 1 week.
Sept 12 - 22		RECOLONIZATION	WITH SHINEFIELD STRAIN	502A			
Sept 26		Skin, nose	Shinefield Strain				
Oct 4		" "	" "				
Oct 15		Nose	" "				
Oct 24		Skin, nose	" "				
Dec 12		Nose	" "				
1967 Mar 3	Nose	Nose	Staph 52/52A/80/81	R		Erythromycin	No sick leave on account of infection.
Mar 21		Nose	Shinefield Strain	S			
June 26		Nose	" "	S			
Sep 9		Nose	" "				
1968 Feb		Nose Lt	Staph 52/52A/80/81	R			
		Rt	" 53/42D	R			
1969 Feb	Eye	Eye	" 52/52A/80/81	R		Orbenim	
1970 April		Skin	Shinefield Strain	S			
		Nose	Commensals only.				