

THE EFFECT OF LOCAL ANTIBIOTIC ON NASAL CARRIAGE OF *STAPHYLOCOCCUS PYOGENES*

By J. C. GOULD

Department of Bacteriology, University of Edinburgh

INTRODUCTION

Large numbers of healthy persons are known to be nasal carriers of *Staphylococcus pyogenes* and are probably the natural reservoir of pathogenic staphylococci in man. Staphylococcal lesions have always been a considerable cause of morbidity in general practice, and since most cases of staphylococcal infection are also carriers, it is probable that infection is frequently autogenous (Gould & Cruickshank, unpublished). Most of these infections are amenable to treatment with antibiotics, but their incidence has not been reduced by the use of these agents. On the other hand, the frequency of staphylococcal infection in surgical and maternity hospitals appears to be increasing, and since many of these infections are due to antibiotic-resistant strains their treatment is often difficult. Means of preventing staphylococcal infection are thus important and have received most attention in hospitals where spread is believed to be due largely to cross-infection from case to case or from carrier to case. However, the reduction of hospital infection with *Staph. pyogenes* by barrier nursing, oiling of blankets, laying of dust, air-conditioning of theatres and wards, and strict attention to aseptic technique, have been at best only partly successful.

Since the ultimate source of infection in both hospital and non-hospital cases must be the nares of carriers it is logical to attempt prevention by reducing the infectivity of the carriers, and this may be achieved by suppressing their staphylococci. The local application of antibacterial agents may temporarily remove the organisms from the surface of the skin of the nares, but, as it is probable that the sweat and sebaceous glands are also colonized, total eradication may not be so easy to accomplish. Some experiments to control nasal carriage of staphylococci have been reported by Delafield, Straker & Topley (1941), Hobbs, Carruthers & Gough (1947) and Moss, Squire & Topley (1948). They found that penicillin-sensitive *Staph. pyogenes* could be cleared from the nose, or reduced in numbers with locally applied penicillin but that re-infection with different strains sometimes took place.

It may be argued that topical administration of antibiotic in this way is undesirable since it has been shown that the use of penicillin is associated with an increase in the number of penicillin-resistant carrier strains (Gould & McKillop, 1954), and the occurrence of antibiotic-resistant staphylococci in hospitals has often been correlated with the amount of corresponding antibiotic used in therapy.

This investigation was designed to find out for how long nasal carriage of *Staph. pyogenes* can be suppressed by the local use of antibiotics, and to assess the likelihood of development of antibiotic resistant strains during treatment.

MATERIALS AND METHODS

Staphylococcal carriers. Persistent nasal carriers among the non-hospital population who had been observed for at least 3 months were chosen; as far as could be estimated they were carriers of only one type of staphylococcus. Antibiotic was given in the form of a lanoline-water cream for topical application. One part of lanoline wax was thoroughly beaten up with two parts of water, and antibiotic solution of the required concentration added. Multiple samples of each batch of cream were assayed to confirm the uniform dispersion and final concentration of the antibiotic. This cream was assayed by the method of Howard (1945) and found to release antibiotic readily to an aqueous environment.

The antibiotic cream was applied several times each day to the skin of the nostrils and rubbed in with the tip of the finger. On the average 25 mg. of cream was applied to the nostril on each occasion. The number of carriers treated was equalled by those not receiving cream. A few were given cream containing no antibiotic.

Examination of the strains of Staphylococcus pyogenes. Nasal swabs from each carrier were examined weekly or more frequently by culture on milk-agar. Colonies of staphylococci were examined for morphology and pigment, and sub-cultures were made in broth to estimate coagulase production, antibiotic sensitivity, penicillinase production and bacteriophage type. Each carrier was examined over at least 20 weeks and representative cultures were periodically kept for comparison with organisms isolated at later stages of the experiment.

RESULTS

Estimation of the minimum effective concentration of antibiotic

Preliminary experiments with penicillin cream showed that a concentration below 1000 units per gram was usually ineffective in producing nose swab cultures free of *Staph. pyogenes*, even during the period of application of the cream. Concentrations up to 10,000 units per gram were increasingly effective. Presumably these higher concentrations are required to overcome loss by absorption, and dispersal, and to leave sufficient antibiotic to kill the organisms on the surface and to penetrate into the glands. Cream containing 100,000 units per gram was not appreciably more effective in clearing staphylococci from the surface of the nares. Similarly, 0.1 % concentrations of streptomycin, chloramphenicol, chlortetracycline (aureomycin) and oxytetracycline (terramycin) were much less effective than 1 % concentrations. Since it has been reported that the development of resistance is more likely after exposure to a high concentration of antibiotic when sterilization is not complete (Gould, Bowie & Cameron, 1953) and since resistance is more likely to appear after prolonged treatment with antibiotic, it was decided to make most of the tests with cream containing 1 % antibiotic, and to limit the period of application to 14 days.

Effect of antibiotic cream on antibiotic-sensitive staphylococci in the nares

In all carriers there was a marked fall in the numbers of colonies of staphylococci isolated from nasal swab cultures taken during the time antibiotic was being applied.

One week after the start of treatment no colonies of *Staph. pyogenes* were isolated from 96 out of 124 carriers. Oxytetracycline was the most effective; *Staph. pyogenes* was absent from nose swab cultures taken from all carriers who had had 1 week's treatment with this antibiotic. In the same way chlortetracycline cleared 86 %; penicillin 77 %; streptomycin 71 % and chloramphenicol 67 %.

Sixty-nine per cent of all the treated carriers gave nose swabs culturally negative for *Staph. pyogenes* for 2 weeks or more after withdrawal of the antibiotic. Forty-nine per cent remained negative for at least 1 month and 26 % for 20 weeks (Table 1). These figures were approximately the same for all the antibiotics used. During the same period the rate of spontaneous change from the carrier to the non-carrier state was 1 % in the control group of carriers who received no antibiotic.

Table 1. *Isolation of Staphylococcus pyogenes from nasal swab cultures following local application of various antibiotics. Occurrence of replacement strains*

1 % antibiotic cream administered 7-14 days	No. receiving antibiotic	No. in whom nasal swab negative for <i>Staph. pyogenes</i>					No. in whom		
		After 1 week's administration of antibiotic	Weeks after withdrawal of antibiotic				Original strain persisted or returned after temporary absence	Replacement strain temporarily present	Replacement strain persisted
			< 1	> 2	> 4	20 or more			
Penicillin	44	34	11	33	20	11	32	16	1
Streptomycin	21	15	6	15	12	6	15	5	0
Chloramphenicol	18	12	9	9	9	6	12	3	0
Chlortetracycline (aureomycin)	21	18	6	15	12	6	15	1	0
Oxytetracycline (terramycin)	20	20	7	13	8	4	16	3	0
Total	124	99	39	85	61	33	90	28	1

Observed changes in antibiotic sensitivity

From twenty-four carriers receiving antibiotic cream, antibiotic-resistant strains of *Staph. pyogenes* were isolated, and these strains were all either of bacteriophage type different from that of the corresponding original carrier strains, or did not react with phage filtrates. Two-thirds of the typable strains belonged to phage group III (Table 2). Replacement with these resistant strains of *Staph. pyogenes* was a temporary episode, except in one carrier receiving penicillin cream in whom the penicillin-resistant strain isolated after withdrawal of the antibiotic persisted during the whole period of observation. In a further four carriers receiving

penicillin cream there was replacement, for a limited period, with a penicillin-sensitive strain of different phage type. In the remaining carriers a strain of the same antibiotic sensitivity and phage type as the original returned after a few weeks, and the resistant strain disappeared.

Table 2. *Bacteriophage type and antibiotic sensitivity of original and replacement strains*

Carrier number	Phage type of		Antibiotic sensitivity	
	Original strain	Replacement strain	Original strain	Replacement strain
	Penicillin (units/ml.)			
6	47A/47C	52	0.03	3
11	3A/3B	76/77	0.03	1.5
16	3A	47A/54	0.04	3
25	47C	47C/45/75	0.06	1.2
39	3A	29/42E	0.03	0.03
44A	52/52A	52A	0.03	2
45	47+	47A	3	0.03
47	47A	51	0.06	0.03
48	51	3B	0.03	0.036
66	3A/51	7/47/54	0.03	3
74	3A/3C	7/47/54	0.06	3
119	52	7/47/54	0.03	1
122	6/47A/54	NT*	0.03	2.25
126	3C/51	6/47/53	0.03	2.25
157	6/7/53	NT	0.03	2
171	52/52A	7/47/53	0.03	3
523	44A/52	NT	0.03	0.03
	Streptomycin ($\mu\text{g./ml.}$)			
411	3B/55	6/7/47/53	0.5	20
415	NT	76/77	1.0	30
420	54	NT	1.0	25
422	3B/3C/51	NT	1.0	25
440	52	NT	0.5	15
	Chloromycetin ($\mu\text{g./ml.}$)			
521	NT	52A	1.5	15
529	52A	NT	3.0	20
530	6/7/53	52A	2.5	20
	Terramycin ($\mu\text{g./ml.}$)			
5	42E/47/47C	47/54	0.25	6
11	52A	NT	0.5	25
43	3A	47/47A	0.2	250
	Aureomycin ($\mu\text{g./ml.}$)			
602	3C/51	NT	0.25	250

* N.T. = not typable.

Suppression of penicillin-resistant carrier strains of Staphylococcus pyogenes

Eight carriers of penicillinase-producing strains of *Staph. pyogenes* were given penicillin cream containing 100,000 units per gram. In four of them the organism disappeared from nose swab cultures for periods of 2-6 weeks; in a fifth there was

apparent replacement with a strain of different phage type which was penicillin-sensitive (Table 2, carrier 45) and in the remaining three the original carrier strain persisted.

Two carriers of penicillin-resistant strains were treated with chlortetracycline cream for 3 days, followed by penicillin cream for 10 days. In both cases the organism was more sensitive to penicillin after exhibition of the aureomycin, but was not suppressed by either antibiotic, although the number of colonies isolated on culture was greatly reduced.

Administration of antibiotic-free cream

Twelve carriers and twelve non-carriers were given antibiotic-free cream for 2 weeks. This had no effect, qualitatively, or quantitatively, on the flora of the anterior nares of any of these individuals.

DISCUSSION

These experiments have shown that the topical application of 1% antibiotic cream was effective in suppressing *Staph. pyogenes* in the human nose for an appreciably longer time than the cream was applied. It is unlikely that the organism ceased to colonize the skin glands of the nares but rather that it was not present on the surface at the time of swabbing. However, even if this was so it is still reasonable to suppose that the staphylococcus was not being passed to other sites on the body, nor disseminated into the air and dust, and therefore that the infectivity of these carriers was reduced.

Thus most of the carriers treated in this series remained in a state of reduced infectivity for about a month after the antibiotic cream ceased to be applied. Recolonization of the surface of the skin of the nares may be followed by further limited courses of similar treatment suitably controlled by bacteriological examinations. In this way staphylococci in the nose may be more or less continuously suppressed for a prolonged period. The justification for this procedure must be a proved reduction in the incidence of staphylococcal infection and this is being investigated both in hospital (Gould & Allan, 1954) and in recurrent staphylococcal infection among non-hospital patients.

The antibiotics tested were more or less equally effective in suppressing antibiotic-susceptible strains of *Staph. pyogenes* in the nose. No carriers of antibiotic-resistant strains, other than a limited number of penicillin-resistant strain carriers, were available for study. A higher concentration of penicillin was fairly successful in suppressing these penicillinase producers and there was evidence that chlortetracycline might be useful in such cases. A likely consequence of this method of treating carriers is that they will become reservoirs of antibiotic-resistant strains. In this particular experiment the end-result was not unfavourable in this respect, since only one carrier, treated with penicillin, was observed to continue carrying a penicillin-resistant strain for more than a few weeks. However, about 20% of the treated carriers were temporarily colonized with antibiotic-resistant strains, an indication that there is some danger that they may spread resistant organisms.

The source of these resistant strains is doubtful. They may have arisen by mutation or adaptation of the parent antibiotic-sensitive strains; but as all of the antibiotic-resistant variants were of different phage type from the sensitive strains in the carriers in whom they appeared this explanation is unlikely, unless the change in antibiotic sensitivity is associated with a change in phage type (Gould, 1955).

A second possibility is that two strains of staphylococci were present in the nares of these carriers, one of greater antibiotic resistance than the other and so favoured by the presence of antibiotic. The carriers in this series were chosen because they appeared to harbour only one strain of well-defined phage type, but the possibility of a second strain being present in small numbers cannot be ruled out.

Thirdly, the resistant strains could have been acquired from the external environment. An antibiotic-resistant staphylococcus deposited on the skin of the nares by inhalation would find conditions favourable for growth, and would be isolated while the sensitive strain was suppressed by antibiotic. Withdrawal of the antibiotic would once again favour the original sensitive strain allowing it to overgrow the resistant strain. Re-establishment of the sensitive strain would be more likely to occur in carriers among the general community who are not continuously exposed to reinfection with antibiotic-resistant organisms, nor to repeated contact with antibiotic, as they would be in hospital environments.

SUMMARY

Lanoline-water cream containing 1% of antibiotic was applied for 7-14 days to the anterior nares of 124 carriers of antibiotic sensitive staphylococci. Nose swab cultures, examined during the administration of the cream, were negative for *Staph. pyogenes* in all carriers who received oxytetracycline, and in 80, 75, 70 and 67% of those who received penicillin, chlortetracycline, streptomycin and chloramphenicol respectively.

Seventy per cent of carriers gave nose-swab cultures negative for at least 2 weeks, 50% for at least 4 weeks and 25% for at least 20 weeks after the cessation of treatment. Over the same period only 1% of a control group ceased to be carriers.

The nares of 20% of carriers receiving antibiotic were temporarily colonized with antibiotic-resistant strains, but in only one case (0.8%) did the resistant organism persist throughout the period of examination.

The use of this method of controlling staphylococcal carriage in preventing staphylococcal infection is discussed.

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