

the lozenges were made known by the makers. The lozenges were made in accordance with the *British Pharmacopoeia* recommendations on penicillin—namely, that each lozenge should contain 500 units of calcium penicillin in a sucrose or sucrose and lactose base. In most cases gum tragacanth was present, about 3–8%, magnesium stearate 0.8–2%, and flavouring agents—e.g., vanillin, essence of lime—in small amounts. All these are substances used in common pharmaceutical practice, and it was felt unlikely that any of them would cause a toxic reaction. As a test of this, lozenges consisting of the base only (blanks) were given to a number of patients, including several who had had glossitis or discoloured tongue with the penicillin lozenges previously. Though the blanks were given for several days, in no case did they produce any toxic effects.

Finally, reactions have been reported when penicillin has been administered in other forms—e.g., inhalation of nebulized aqueous solutions (Mutch, 1947) and continuous intranasal drip (Royston, 1947). In addition, both types of reaction were observed in patients treated with crystalline G lozenges and pastilles; these contained about 96% of penicillin G, 4% of the other penicillins, and no impurities.

In many cases of reaction to penicillin the mouth cavity, as tested by the salivary count, was either sterile or contained coliform organisms. In a number of cases, however, *Pseudomonas pyocyanea*, Friedländer's bacillus, *Proteus vulgaris*, and *M. albicans* were present. From the two tables it will be seen that the average reaction to penicillin began on the fourth day of treatment, but sometimes did not begin for seven or even nine days. In most cases treatment had been carried out for three or more days—i.e., beyond the point (48 hours) where the oral flora had changed completely to penicillin-insensitive organisms. Symptoms usually diminished in two days from the time of ceasing penicillin therapy, but persisted to a lesser degree for about a week, and occasionally longer.

Of the less common symptoms, lack of salivation, ageusia, and a capacity to taste penicillin after cessation of treatment are the most striking.

Summary and Conclusions

A review of the reported cases of oral reaction to penicillin used locally in the mouth is given, together with an account of similar cases among patients treated in the dental department at Guy's Hospital.

Neither nicotinamide deficiency nor the lozenge base is responsible for these oral reactions.

It is noticed that reactions do not occur until there has been a complete change in the character of the oral flora. This takes about 48 hours, and it seems reasonable to limit the use of penicillin for the treatment of oral infections to this length of time as a rule. To maintain an adequate and continuous concentration of penicillin in the mouth the use of this antibiotic in chewing-gum, 10,000 units per piece, thrice daily, is suggested.

I would like to thank Dr. C. Shuttleworth, assistant dental bacteriologist, for numerous salivary counts and helpful advice; the many dental students who so kindly co-operated in this investigation; and Mr. Gott, of the dispensary, for overcoming the technical difficulties inherent in the preparation of penicillin chewing-gum.

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CARRIAGE OF PENICILLIN-RESISTANT STAPH. PYOGENES IN HEALTHY ADULTS

BY

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The number of papers on this subject that have appeared in recent years indicates that there may be an increase in resistance to penicillin among strains of *Staph. pyogenes* isolated at different times from human infections during the course of penicillin treatment (Rammelkamp and Maxon, 1942; Anderson *et al.*, 1944; Bondi and Dietz, 1945; Gallardo, 1945; North *et al.*, 1946). On the other hand, there is also evidence that strains of *Staph. pyogenes* exist which are naturally resistant to penicillin, having been isolated before the institution of penicillin treatment and in many instances having been shown to possess the power of inactivating penicillin by the production of penicillinase (Kirby, 1944; Spink *et al.*, 1944a, 1944b; Bondi and Dietz, 1945; Gots, 1945; Gallardo, 1945; Harley *et al.*, 1946).

Further, it has been shown by Barber (1947a, 1947b) that the incidence of infection with penicillin-resistant strains may be increasing, since in one hospital the percentage rose from 14.1 in 1946 to 38 in 1947. There is thus evidence not only that some strains of *Staph. pyogenes* are resistant to penicillin and that some may become resistant in the course of treatment but also that the incidence of infections with such strains may be increasing.

The nose and skin of normal persons have been shown by many earlier workers to be reservoirs of considerable importance for the carriage of potentially pathogenic staphylococci (for studies and references to earlier work see the papers of Miles *et al.*, 1944; Williams, 1946).

Investigations of outbreaks of staphylococcal infections have shown that the nose, throat, and skin of persons in the patient's environment, or of the patient himself, harboured strains of the same phage or serological type as the infecting strain (Allison and Hobbs, 1947; Hobbs *et al.*, 1947).

So far as we are aware there has been no published work concerning the incidence of penicillin-resistant strains of *Staph. pyogenes* occurring in the nose and throat and on the skin of normal persons, although Moss *et al.* (1948), in an investigation in 1946, encountered one resistant strain and one partially resistant strain in the noses of 21 patients who were persistent nasal carriers of *Staph. pyogenes*.

In view of the evidence in support of the nose and skin as reservoirs of strains able to cause infection, it is obviously important to investigate the incidence of strains resistant to penicillin in these situations. Opportunity was taken, therefore, to examine the penicillin-resistance of all coagulase-positive strains of staphylococci isolated from the nose, throat, saliva, and six skin sites of 50 healthy individuals during the course of a different investigation.

Following the practice of earlier workers, we have applied the term *Staph. pyogenes* to all coagulase-positive staphylococci irrespective of pigmentation.

Isolation of Strains

The group, studied between April and November, 1947, consisted of 50 volunteer male medical students and laboratory workers. One-half of these were students not engaged

in clinical work and laboratory staff not primarily handling material likely to be infected with *Staph. pyogenes*. None of the volunteers was infected clinically.

Nine sites were swabbed in the following manner:

Throat.—A dry cotton-wool swab was rubbed over the tonsils and the posterior pharyngeal wall.

Nose.—A swab moistened with broth was passed into both anterior nares.

Saliva.—A dry swab was dipped into a pool of saliva allowed to collect between the gum and lower lip.

Skin.—This was sampled on the following six sites by rubbing a swab moistened with broth over an area the size of a penny with a circular motion 20 times: (1) *Face*: both malar prominences. (2) *Hand*: palmar surface of the right hand. (3) *Chest*: middle third of the sternum. (4) *Abdomen*: immediately above the umbilicus in the midline. (5) *Back*: over the lumbar vertebrae. (6) *Leg*: over the right patella.

All swabs were immediately inoculated into "lemco" broth and incubated aerobically overnight. The following day subcultures were made from the broth on to horse-blood-agar plates, which were then incubated overnight and examined the next day for colonies of staphylococci. Where there were any differences—e.g., in pigmentation, presence or absence of haemolysis, etc.—representative colonies of each variety were picked. The colonies thus picked off were subcultured on to segments of a lemco-agar plate and incubated overnight. Films were made the next day and stained by Gram's method, and strains which did not show the typical morphology of the staphylococcus were discarded. The plates were allowed to remain on the bench for three days to enable pigment production to be recorded, and the strains were then subcultured into agar "stabs" and stored at 4° C. A total of 340 strains were isolated.

All strains were then examined for the production of coagulase, using the tube technique as described by Gillespie (1943). This test was used as the sole criterion of potential pathogenicity, as earlier work has shown it to be the simplest and most reliable single test for pathogenicity among staphylococci. Of the 340 strains examined 83 (24.4%) were found to be coagulase-positive.

Carriage of *Staph. pyogenes*

The details of carriage of the 83 strains of *Staph. pyogenes* among the 50 individuals are shown in Table I.

TABLE I.—Carriage of *Staph. pyogenes* Among 50 Healthy Adults

Site of Carriage	No. of Carriers	% of Whole Group	% of 31 Carriers
Nose	20	40	64.4
Throat	9	18	29.0
Saliva	2	4	6.4
Face	14	28	45.1
Hand	7	14	22.5
Chest	9	18	29.0
Abdomen	7	14	22.5
Back	2	4	6.4
Leg	4	8	12.8
No. of carriers	31	62	
Nose or throat only	10	20	32.2
Skin only	7	14	22.5
Combined nose or throat or saliva and skin	14	28	45.1

On each of nine sites in five individuals there were isolated two different strains of *Staph. pyogenes* as judged by colonial appearance.

The findings shown are similar to those of Williams (1946), who surveyed a comparable group of 50 students by sampling the nose only, together with 11 skin sites, using somewhat similar cultural methods. There is, however, some disparity between our findings and those of Williams concerning the prevalent site of carriage in those

who are not simultaneous nasal and skin carriers. In our series, of the 17 persons from whom *Staph. pyogenes* was isolated from either skin or nasopharynx, but not from both, in 10 (58.8%) the organism was found in the nasopharynx only and in 7 (41.2%) on the skin only. Williams, however, found among 19 such persons that only 3 (15.7%) were nasal carriers, while 16 (84.3%) were skin carriers.

The numbers examined in both series are small and the discrepancies are possibly due to the fact that Williams examined 11 skin sites but not the throat and saliva, whereas we studied six skin sites but also examined the throat and saliva.

Penicillin Resistance

The 83 coagulase-positive strains isolated in the above investigation were next examined for penicillin resistance, using in the first instance the ditch-plate method with a concentration of 10 units of penicillin per ml. of agar in the ditch: 15 strains (18%) were found to be resistant by this method.

These strains were next retested by the serial dilution method in broth, using serial dilutions of penicillin in 0.5-ml. amounts of broth. The inoculum was one drop (0.02 ml.) of a 1 in 100 dilution of a 24-hour broth culture. Our results are shown in Table II.

TABLE II.—Degree of Penicillin Resistance

No. of Times More Resistant than the Oxford Staphylococcus	No. of Strains
128	4
64	1
32	6
16	3
8	1
Total	15

The 15 resistant strains were carried by six members of the group studied. One of the six subjects (REE) was found to be carrying on a number of sites two strains of *Staph. pyogenes* differing in their colonial appearance. One strain (R2), occurring on two sites, had a resistance 128 times that of the Oxford staphylococcus, and the other (R1), occurring on three sites, had a resistance 32 times greater than that of the Oxford strain. It is impossible, without the help of methods of identification, such as serological or phage typing, to decide whether these two apparently different strains are in fact different or whether they represent mutants from a single parent strain.

Only one (LUM) of these six persons had ever had penicillin treatment; he once had some penicillin lozenges. Details of the carriage are shown in Table III.

TABLE III.—Carriage of the Penicillin-resistant Strains Isolated

Carrier	Sites								
	Nose	Throat	Saliva	Face	Hand	Chest	Abdomen	Back	Leg
SAY	R	—	—	R	—	—	—	—	—
LUM	S	—	—	S	S	—	—	—	—
PER	S	—	—	S	—	—	—	—	—
REF	R1, R2	R1, R2	—	R1	—	—	—	—	—
COR	—	—	—	R	—	—	R	R, S	S
BES	R	R	—	—	—	—	—	—	—
No. of carriers	3	3		3		1	2	1	

The carrier rate of resistant strains among 50 healthy adults is 12%, that among 31 healthy carriers of *Staph. pyogenes* 19.4%.

R = Resistant strain.
S = Sensitive strain of *Staph. pyogenes*.
R1 and R2 = Strains isolated from same individual with marked differences in degree of resistance.

Discussion

In the 50 healthy adult males investigated the rate and distribution of carriage of *Staph. pyogenes* were similar to those found by earlier workers in groups of healthy

adults. The foregoing observations are comparable to those reported by Williams (1946) in a group of the same number and of similar occupation.

Of the group of 50 persons, 6 (12%) were carriers somewhere on their persons of strains of *Staph. pyogenes* resistant to penicillin. This comprises nearly one in five, or 19.4%, of the 31 persons who were carriers.

These figures are disturbingly high, although not perhaps unexpected in view of the apparently increasing incidence of penicillin-resistant strains in human infections. We are, however, not in a position to assess whether there has been an increase in the carrier rate of resistant strains comparable to that found in the incidence of strains isolated from infections, for we have not been able to discover any published work in this connexion. Moss *et al.* (1948), who were endeavouring during 1946 to abolish nasal carriage of *Staph. pyogenes* by the intranasal administration of penicillin to 21 patients who were persistent nasal carriers, encountered one case which yielded a penicillin-resistant strain and one case which yielded a partially resistant strain during the course of treatment. Neither of these strains, however, was able to produce penicillinase.

We are able to confirm the findings of others (Kirby, 1944; Bondi and Dietz, 1945; Gots, 1945; Barber, 1947a, 1947b) that these naturally occurring resistant strains are able to inactivate penicillin.

Summary

Swabs from the nose, throat, saliva, and six skin sites of 50 healthy men showed a carrier rate of 62% for coagulase-positive staphylococci.

Examination of the 83 coagulase-positive strains isolated showed that 15 (18%) penicillin-resistant strains were being carried by six persons (12%).

Among the 31 carriers of coagulase-positive staphylococci the carrier rate for resistant strains was thus 19.4%.

The resistant strains were all able to inactivate penicillin.

The significance of the findings is discussed.

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INFECTED HANDS TREATED WITH SYSTEMIC PENICILLIN

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In an attempt to assess the value of systemic treatment penicillin was given as a routine to all out-patients attending the Infected Hands Clinic at the London Hospital from November, 1946, to January, 1948.

Method

Systemic Penicillin.—One intramuscular injection of penicillin, 200,000 units in aqueous solution (100,000 units per ml.), was given each day. The only variation in dosage was a reduction to 100,000 units in small children and a rise to 300,000 units for the first two or three days of a severe infection with systemic reaction.

Local Dressings.—Penicillin cream (500 units per gramme in an emulsifying wax and castor-oil base) was applied. Glycerin and magnesium sulphate paste was also used extensively in the presence of slough and during the course of systemic penicillin, local chemotherapy being of little value in the presence of necrotic tissue. Repeated saline or antiseptic baths were never used, but occasionally a hypertonic saline bath enabled one to remove a dry adherent dressing, drain, or scab under which pus was collecting. The drains were sterile ribbon gauze dipped in penicillin cream, which achieved the effect of local penicillin with the minimum of difficulty. Splints were never used except in cases of arthritis or tenosynovitis, because it was felt that the bulky dressing applied after incision, combined with a sling, gave adequate rest for the first 48 hours, and that after this time active movements were desirable. Dressings were done on an average every second day.

Physiotherapy.—No short-wave diathermy or dry heat was given. The great majority of patients did not attend the physiotherapy department. All cases with much sloughing of the pulp or osteomyelitis attended a class for finger exercises and occupational therapy.

Incision.—General anaesthesia—gas, oxygen, with occasionally "trilene"—was used, and in many cases an avascular field was ensured by a rubber tubing tourniquet round the base of the finger. Local nerve-block with procaine was employed occasionally. Ethyl chloride spray was not used.

The selection of alternate cases as controls being impracticable, the records of the previous six months are presented for comparison, as well as those of six months in 1944. The type of infection are dealt with below.

I. Paronychia

Surgery.—In early cases a unilateral incision was made in the angle of the nail fold. Usually the incision was bilateral, raising a dorsal flap and removing part or all of the nail according to the extent of the infection. A drain was left under the flap for 48 hours.

The results of treatment with penicillin are given in Table I.

Conservative Treatment.—For 12 out of 134 cases no incision was necessary, inflammation resolving with local heat and penicillin. The average length of history was 3.3 days (10 cases).

Operative Treatment.—Usually pus had already formed when the case was first seen. Incision was then necessary. A preliminary review of cases after 50 to 60 patients had

The Scientific Film Association has issued a useful pamphlet entitled "On Organizing Medical Film Programmes" (price 1s. from the Association, 34, Soho Square, London, W.1). Notes on such practical details as how to arrange the chairs, making sure that the fuses are readily accessible, providing a firm table for the projector, and choosing colour or monochrome films are included, and there is a short summary of the law in relation to showing films.