

sensitive to less than 1 unit of penicillin per ml., whereas a large inoculum grew in from 12.5 to 50 units per ml. Thus the heaviness of the infection is the most important factor in deciding whether a patient infected with such an organism will benefit by penicillin treatment. As it is usually impossible to determine this, elaborate laboratory tests designed to show degree of sensitivity or rate of penicillinase production are valueless. It should further be emphasized that where a small inoculum is used in testing penicillin sensitivity the type of resistant organism here described may easily be missed.

The differentiation of pathogenic from non-pathogenic staphylococci in the laboratory has received considerable attention lately. Schwabacher, Cunliffe, Williams, and Harper (1945) and Christie, North, and Parkin (1946) found a small number of strains which were coagulase-positive but did not produce  $\alpha$ -lysin, and both sets of workers considered the latter test to be more closely correlated with pathogenicity. In the present investigation all 111 strains were coagulase-positive and 105 were  $\alpha$ -toxigenic. Although no evidence could be obtained to indicate that the  $\alpha$ -lysin-negative strains were less pathogenic than the others, none of them came from very serious cases of infection.

### Summary

Out of 100 cases of infection with *Staph. pyogenes* occurring in this hospital 35 yielded penicillin-resistant strains. In 24 cases all colonies tested were penicillin-resistant and in 11 both sensitive and resistant strains were isolated.

All penicillin-resistant strains were shown to destroy penicillin. Seventeen were tested for penicillin sensitivity, using two different-sized inocula, and it was found that whereas a small inoculum was sensitive to from 0.06 to 4 units per ml. a large inoculum grew in from 12.5 to 50 units per ml.

Twenty-four of the 35 penicillin-resistant strains were shown to belong to phage group 6/7/47, whereas only nine of 76 penicillin-sensitive strains fell into this group. When 140 penicillin-resistant strains isolated from patients in a variety of hospitals were phage-typed, 85 were found to belong to the 6/7/47 group.

All strains were initially sensitive to streptomycin. A strain from one patient became resistant after five days' treatment with this antibiotic.

Twenty-one of the 111 strains were resistant to sulphathiazole, and 17 of these were also resistant to penicillin.

All 111 strains were coagulase-positive; 105 were  $\alpha$ -toxigenic.

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## INFECTION WITH PENICILLIN-RESISTANT STAPHYLOCOCCI IN HOSPITAL AND GENERAL PRACTICE

BY

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The isolation of penicillin-resistant staphylococci from clinical sources, at one time a rare event, is now a commonplace. The great majority of these strains possess a natural resistance to penicillin by virtue of their ability to produce a penicillin-neutralizing enzyme, penicillinase (Kirby, 1944; Bondi and Deitz, 1945). Some indication of the frequency with which penicillinase-producing staphylococci are encountered in hospital practice, and the rising proportion of staphylococcal infections due to these strains, can be gauged from the work of Barber, who recorded a progressive increase in the incidence of infections with resistant strains from 14.1% in 1946 to 59% in 1948 (Barber, 1947a, 1947b; Barber and Rozwadowska-Dowzenko, 1948).

Dr. Barber's work has aroused much interest and not a little alarm, for at first sight it might appear that the power of penicillin in combating staphylococcal infection is decidedly on the wane. However, the results of an investigation carried out in a large hospital are not necessarily representative of the community as a whole, an opinion to which Dr. Barber herself subscribes when she states (Barber and Rozwadowska-Dowzenko, 1948): "Though penicillin-resistant strains of *Staph. pyogenes* are now appearing with increasing frequency in many hospitals, this is probably not the case in the community at large." This statement receives substantiation from the results of an investigation carried out at this hospital during the past 12 months.

### Outline of Investigation

Staphylococci isolated on routine culture were in the first instance tested for coagulase-production by the method of Gillespie (1943) and sensitivity to penicillin on ditch-plates, using 10 units of penicillin per ml. of agar in the ditch. Coagulase-positive strains were then subcultured and set aside for further investigation, including a quantitative estimation of penicillin sensitivity (using serial dilutions of penicillin in 1-ml. amounts of broth and an inoculum of 0.02 ml. of a 1 in 100 dilution of a 24-hour broth culture), production of penicillinase, and sensitivity to streptomycin.

In the meantime further information regarding the source of the specimens which yielded coagulase-positive staphylococci was obtained by questioning patients and nursing staff, and in some cases examining the lesions from which the specimens were obtained. In particular it was noted whether the patient was an in-patient or out-patient not only at the time the specimen was collected but also at

the time that infection first became apparent, and whether the patient was having or had had penicillin treatment. Finally, attention was paid to the nature of the specimens submitted for examination, and to the amount and purity of growth on primary isolation, with a view to ensuring that the staphylococci were both pyogenic and truly pathogenic. As one would expect from the mode of selection, the great majority of strains accepted for analysis were from specimens of frank pus or purulent material from boils, abscesses, septic fingers, infected wounds, etc., and in nearly all cases the growth of staphylococci on primary culture was heavy and pure.

#### Analysis of 120 Strains of *Staph. pyogenes*

One hundred and twenty strains of *Staph. pyogenes* from the same number of patients were investigated. All but three were of the aureus variety; the three albus strains were strongly coagulase-positive on repeated examination, were present in pure culture on primary isolation, and the source of the strains left no doubt that they had been actively pathogenic. Of these 120 strains 73 (60.8%) were sensitive to penicillin and 47 (39.2%) resistant. The sensitive strains possessed a degree of sensitivity approximately equal to that shown by the control Oxford staphylococcus, and none produced penicillinase. On the other hand, all the resistant strains were penicillinase-producers. The resistance was gross in all cases both when tested on the ditch-plate (growth extending up to and over the ditch) and when estimated quantitatively, the minimal concentration of penicillin required to inhibit growth varying from 5 to 400 times that required to inhibit the control strain of Oxford staphylococcus (Table I).

TABLE I.—Degree of Resistance of 41\* Resistant Strains

No. of strains	Inhibiting Concentration of Penicillin in Units per ml.							
	32	16	8	4	2	1	0.8	0.4
.. ..	1	3	5	9	7	2	6	8

\* Six strains were not available for quantitative sensitivity tests. *Staph. aureus* (Oxford) was inhibited by 0.08 unit per ml.

Resistance to streptomycin was not encountered among any of these 120 strains, all possessing a sensitivity to this antibiotic of the same order as the control Oxford staphylococcus.

#### Analysis of 78 Out-patient and In-patient Strains

A separation of the 120 strains into those derived from out-patients and those from in-patients was then attempted. Inevitably a number of strains could not be placed in either of these categories. Thus a specimen may have been received from an in-patient, but the history of the case indicated that infection had occurred before the patient was admitted to hospital. Conversely, an out-patient may have given a history of a recent stay in hospital for the treatment of the condition from which he was suffering at the time the out-patient specimen was collected. Such cases in which the origin of the infecting strain was not clearly established have been omitted from this part of the analysis. Altogether 42 strains were unclassifiable, leaving a total of 78 strains which could be labelled with confidence "out-patient" or "in-patient" strains. The incidence of sensitive and resistant strains for this reduced series was 60.25% and 39.75% respectively, indicating that the exclusion of these 42 unclassifiable strains had not resulted in any significant deviation from the ratio for the original series, which was 60.8% sensitive to 39.2% resistant.

**Out-patient Series.**—The 40 strains which comprised the out-patient group were derived from specimens collected in the casualty and out-patient departments of this and neighbouring hospitals, and from specimens sent in by local practitioners. All but five of these strains were highly sensitive to penicillin, representing an incidence of sensitive strains of 87.5% and of resistant 12.5% (Table II).

TABLE II.—Incidence of Penicillin-resistant *Staph. pyogenes* from 78 Patients with Staphylococcal Infection

Source	No. of Strains	Resistant Strains
Out-patients .. .. .	40	5 (12.5%)
In-patients .. .. .	38	26 (68.4%)

**In-patient Series.**—Strains accepted for this series were recovered from patients whose infection had arisen during their stay in hospital. Thus infected operation wounds, infected plaster sores and bedsores, and neonatal infections were among the lesions which yielded in-patient strains. Of the 38 strains in this group no fewer than 26 (68.4%) were resistant, and 12 (31.6%) were sensitive. When these resistant strains were further analysed it was found that 11 of the 26 had originated in one department of the hospital, the maternity unit. This finding prompted a search for a carrier among the staff of the unit, and one of the senior nurses was found to be a persistent heavy nose-and-throat carrier of a penicillin-resistant coagulase-positive *Staph. aureus*. Phage-typing of eight patient strains, two carrier strains, and three strains isolated from the ward dust by exposing blood-agar plates was carried out through the courtesy of Dr. R. E. O. Williams at the Central Public Health Laboratory, Colindale. The results (Table III) show

TABLE III.—Phage Reactions of Resistant Strains from Maternity Unit

Ref. No.	Source	Phage Reaction	Remarks
50	Pemphigoid impetigo. Pustular rash	3A	
73	Ophthalmia neonatorum ..	3A	
77	Pustules on nipple .. ..	3A	
87	" " " " " " " " " "	47+	
94	Ophthalmia neonatorum ..	3A	
95	Pustular rash. Pemphigoid impetigo	47+	Child of No. 101
101	Pustular rash .. .. .	47/47B+	Mother of No. 95
108	Ophthalmia neonatorum ..	47/47B+	
49	Nose and throat of Nurse 1 ..	3A	Heavy persistent carrier
78	Nose and throat of Nurse 2 ..	52A	Temporary carrier
79	Ward dust, Colony 1 .. ..	3A	
80	Ward dust, Colony 2 .. ..	7	
97	Ward dust, Colony 3 .. ..	47/47B+	

that all of the patients were infected with staphylococci belonging to one of two phage-types, that these same types were isolated from the ward dust, and that one of them (type 3A) was carried by a member of the nursing staff.

#### Effect of Previous Penicillin Therapy on the Resistance Rate

A history of treatment with penicillin for several days before the collection of the specimens was obtained from 41 patients. Twenty-five strains from these penicillin-treated patients were resistant and 16 were sensitive. Of 51 strains from patients not treated with penicillin 22 were resistant and 29 sensitive (Table IV). In short, the incidence

TABLE IV.—Penicillin Therapy and Resistance Rate

Source*	No. of Strains	Resistant Strains
Untreated patients .. .. .	51	22 (42%)
Treated patients .. .. .	41	25 (59%)

\* The 92 patients which comprise this series include both out-patients and in-patients, and are independent of those quoted in Table II.

of resistant strains was slightly but not significantly higher in patients receiving penicillin.

In interpreting these findings it should be remembered that 42 of the 47 resistant strains were hospital strains, and, although they were isolated from 42 patients, it cannot be said that they were all distinct strains, for, as phage-typing has shown, dissemination of any one strain or the descendants of that strain by means of cross-infection had probably occurred to some extent. Consequently a number of the infecting strains were already resistant before the institution of penicillin treatment. All five out-patients and 20 in-patients from whom resistant strains were isolated were on large doses of penicillin when the specimens were collected. It is conceivable that the cells of the original infecting strain were for the most part susceptible, but that a number of variants within the strain enjoyed a measure of resistance. By the time the specimens were collected penicillin had eliminated the susceptible cocci, leaving a flora which was resistant.

### Discussion

There is no doubt that staphylococcal infections due to penicillin-resistant strains are being encountered with increasing frequency in hospital practice. The reason for this unwelcome trend would seem to lie in the fact that the staphylococcal population of most hospitals at the present time is dominated by strains which possess a natural resistance, the inevitable consequence of the widespread use of penicillin during the past few years. By a process of natural selection these resistant strains have survived and propagated at the expense of susceptible breeds; and their presence in ward dust and the upper respiratory passages of members of the hospital staff, together with case-to-case infection, no doubt accounts for the high incidence of this type of infection in hospitals. By contrast, the environmental conditions which prevail in the community at large offer small scope for the perpetuation and dissemination of resistant strains, and one would anticipate a much lower incidence of infection due to these strains among the general population.

The carrier rate of penicillin-resistant staphylococci among hospital and non-hospital employees is under investigation and will be the subject of a later communication. Preliminary findings indicate that the rate of carriage of these strains by members of the staff of this hospital is disturbingly high. Of 50 ward nurses no fewer than 23 (46%) were found to carry in their anterior nares coagulase-positive *Staph. aureus* resistant to at least 1 unit of penicillin. The resistant strains all produced penicillinase. Of a control group of 50 office workers (not attached to the hospital) only one (2%) was found to be a nasal carrier of a penicillin-resistant strain.

From these and other observations one might attempt a grouping of staphylococcal infections according to the sensitivity to penicillin of the infecting strains, as follows. (a) Infection due to a pure sensitive strain the cells of which are all susceptible to the action of penicillin in adequate dosage. The majority of infections, especially those met with in general practice, fall into this group. (b) Infection due to a pure resistant strain—for example, hospital infection—which is naturally resistant to penicillin. (c) Infection due to a single strain, for the most part sensitive but containing a variable number of naturally resistant penicillinase-producing variants. Under the influence of penicillin such a strain may develop into a pure resistant strain owing to the elimination of penicillin-susceptible cells (Anderson *et al.*, 1944; Spink and Ferris, 1947). (d) Infection due to a sensitive staphylo-

coccus complicated by superinfection with an insensitive strain of different phage type (Barber, 1947a, 1947b).

Recent reports on the high incidence of resistant strains have cast doubt on the competence of penicillin to deal with staphylococcal infections (leading article, *British Medical Journal*, 1947, 2, 874). The results of this study are presented in the hope of restoring confidence in penicillin for the treatment of staphylococcal infections in general practice. So far as the results of a limited study confined to one provincial hospital area are applicable to the general situation, it would seem that intelligent therapy with penicillin (and other measures when indicated) should effect a cure in nine of ten out-patients with staphylococcal sepsis. At the same time the results confirm the high proportion of hospital infections due to resistant strains: only one in every three patients with infection contracted during their stay in this hospital was eligible for penicillin therapy.

Penicillinase-producing strains of staphylococci are fully pathogenic (North and Christie, 1946; Barber, 1947a) and on occasion are capable of causing severe and sometimes fatal infections, such as staphylococcal septicaemia. Since resistance to penicillin appears to be specific, and not necessarily accompanied by resistance to either sulphonamides (Spink, Hall, and Ferris, 1945) or streptomycin, recourse may be had to one or both of the latter anti-staphylococcal agents in the treatment of severe infections due to penicillin-resistant staphylococci.

### Summary

Seventy-eight strains of *Staph. pyogenes* from clinical sources have been analysed according to their sensitivity to penicillin. The resistance rate of strains derived from out-patients was 12.5% and from in-patients 68.4%.

All resistant strains produced penicillinase.

Many of the strains were already resistant before penicillin treatment was started.

The epidemiological and clinical significance of these findings has been briefly discussed. The frequency with which penicillin-resistant strains are carried in the anterior nares of ward nurses is thought to be partly responsible for the high proportion of hospital infections with resistant staphylococci.

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The June report of the British Control Commission for Germany says that the Rockefeller Institute has arranged a study tour in Denmark, England, and the U.S.A. for a number of young German medical officers of health, two of whom will probably come from the British Zone. The tour will last two to three months. In the hope that the proposed central narcotic administration for Western Germany may be modelled on British organization, arrangements are being made to send prospective officials to Britain for a 10-day visit to study British methods. No special shortages of medical supplies were reported during the month. Improvement in the supply of penicillin should enable a reserve to be built up again, and it is now sold more cheaply.