sulphamezathine and sulphamerazine, the advantage seems to lie with sulphamerazine, though it has still to be proved that the frequency of relapses with this drug will be less than with sulphamezathine. Contrary to expectation, the combined use of penicillin locally and sulphonamide orally does not seem to reduce the relapse rate, but it should always be borne in mind that relapses are sometimes, possibly often, reinfections rather than relapses in the true sense.

Routine Procedure for Treatment

The steps in the two alternative methods of treating ophthalmia neonatorum available at present—sulphonamides orally and penicillin locally—may be thus summarized:

(a) *Steps in Common for the Two Methods.*—On admission a swab is taken for smear and culture and the eye is irrigated with half-normal saline at room temperature. A drop of adrenaline 1 in 1,000 is instilled and a scraping is taken from the palpebral conjunctiva for examination for the presence of inclusion bodies. Gutt. atropinae sulphas, 1%, are instilled if the cornea is affected. Any pus that may have accumulated is wiped away with moist pledgets of cotton-wool.

(b) *Procedure for Sulphonamide Treatment.*—(1) After the preliminary measures a tablet of sulphamerazine or sulphamezathine (0.5 g.) crushed into powder is given by mouth in a teaspoonful of water or milk. Alternatively a stock mixture can be used. (2) Sulphamerazine administration in doses of 0.25 g. is continued every eight hours. If sulphamezathine is used the administration has to be at six-hourly intervals. (3) Local treatment consists of three-hourly irrigation with saline solution during the first day in cases with profuse discharge; as a rule there is no need for further irrigation on the subsequent days. After irrigation medicinal paraffin is instilled as a precaution against the sticking together of the lids. (4) Atropine is instilled three times daily in cases with corneal haze or ulceration. (5) Sulphonamide administration is continued for 48 hours after clinical cure.

With this treatment swelling of the lids generally subsides within 12 hours after admission; purulent discharge disappears within 24 hours.

(c) *Procedure with Local Penicillin Therapy.*—(1) The preliminary measures are completed by the instillation of a drop of penicillin in a concentration of 10,000 units per ml. into the conjunctival sac. (2) The baby is now placed on the nurse's lap, while another nurse sitting near by instils one drop of penicillin solution, 10,000 units per ml., every minute for 30 minutes. Irrigation is not needed, as pus does not form to any extent; such thin mucoid discharge as is present can be ignored or, if it clings to the lid margin, wiped away with moist pledgets of cotton-wool. (3) At the end of this time there is invariably no pus and generally little or no discharge. The eye, however, is still moist, the lids are still swollen, and the lid margins tend to be sticky. The baby is returned to its cot, and instillation of penicillin drops is continued six times at five-minute intervals, followed by a similar number of instillations at half-hourly, hourly, and two-hourly intervals. This gives a total of 22 hours' treatment. Many cases require no further attention. (4) In some babies the lid margins still tend to remain sticky. It is advisable in such cases to continue with penicillin at two-hourly intervals until the eye is dry, when treatment is carried on for a further 12 hours.

Crystalline penicillin only should be used for making up the drops. Impure penicillin is likely to cause irritative reactions.

Summary

A series of 151 cases of ophthalmia neonatorum treated by several different methods is recorded.

Oral administration of doses of 200,000 units of penicillin, either exclusively or after an initial intramuscular injection, has proved disappointing.

Combined oral sulphonamide and local penicillin therapy proved effective in reducing the duration of treatment but ineffective in reducing the considerable frequency of relapses seen with either sulphonamide or penicillin therapy.

Duration of treatment was likewise reduced by increasing the dose of sulphonamide. With sulphamezathine, 0.5 g. initially and a maintenance dose of 0.25 g. six-hourly, some 70% of cases showed clinical cure within one to three days. Similar results were obtained with sulphamerazine, 0.5 g. initially and 0.25 g. at eight-hourly intervals. The use of these larger doses of sulphonamide does not apparently influence the relapse rate; it is, however, possible that sulphamerazine may prove to be a favourable exception.

For the present the best way of administering penicillin is still the instillation of drops of 10,000 units per ml. initially at intervals of a minute for half an hour and subsequently at less frequent intervals. For the best results with sulphonamide therapy higher doses than those used previously are necessary.

We are indebted to the matron of White Oak Hospital and Sister Condon, of the Ophthalmia Neonatorum Unit, for their loyal help in the treatment of the cases recorded here.

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BACTERIOPHAGE TYPES IN PENICILLIN-RESISTANT STAPHYLOCOCCAL INFECTION

BY

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AND

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Many studies concerning the incidence of penicillin-resistant staphylococcal infection have been reported, and it is now generally agreed that this is increasing (Spink *et al.*, 1944, 1945; Bondi and Dietz, 1945; Gallardo, 1945; Plough, 1945; Harley *et al.*, 1946; Barber and Rozwadowska-Dowzenko, 1948). Results of investigations of a series of infections occurring in a single hospital, however, are difficult to assess, as such institutions often seem to be breeding-grounds of a particular strain of pathogenic staphylococcus. Thus in previous studies in a single hospital by one of us (Barber, 1947a, 1947b; Barber and Rozwadowska-Dowzenko, 1948) it was found that 59 of 100 cases of staphylococcal infection investigated in 1948 yielded penicillin-resistant staphylococci, whereas the incidence in a similar series was 38% in 1947 and 14.1% in 1946. Each year, however, it was found that a significantly high proportion of the penicillin-resistant strains when typed by the bacteriophage method fell into the 6/47 group, suggesting that most of the penicillin-resistant infections might have been caused by a single strain of staphylococci.

Recent experience, however, has led us to the conclusion that a large number of penicillin-resistant staphylococci isolated from infections in widely separated hospitals belong to the 6/47 phage group. In the present investigation, therefore, staphylococci isolated from a series of 100 cases of infection occurring in this hospital have all been tested for penicillin sensitivity and phage-typed to see if the two could be correlated.

Methods

During the investigation all cultures of staphylococci (usually on blood-agar plates) obtained from cases of infection were collected from the routine laboratory. From each primary plate 10 colonies were picked off and streaked on to penicillin ditch-plates, the ditch containing 10 units of penicillin per ml. The remaining growth was then emulsified in broth and plated out on a similar penicillin ditch-plate in order to detect small numbers of penicillin-resistant organisms which might otherwise have been missed. After incubation overnight the plates were examined. If all colonies from a single specimen showed a similar reaction to penicillin one was picked off into "lemco" broth for further investigation. If penicillin-sensitive and penicillin-resistant staphylococci were present, one colony of each was similarly picked off.

All staphylococci were tested for coagulase by the slide method and only coagulase-positive strains included in the series. Later all strains in the series were tested for haemolysin production by the method of Gillespie and Simpson (1948), and strains giving doubtful or negative results were tested for coagulase production by the tube method of Fisk (1940) and for haemolysin by the method described by McFarlan (1938).

All penicillin-resistant strains were tested for penicillinase production by the method described by Barber (1947a); 17 of them were tested by the serial dilution method in broth, using two different-sized inocula in each case, as recommended by Gilson and Parker (1948). Sensitivity to streptomycin was also tested on ditch-plates, the ditch containing 100 units of streptomycin per ml., and to sulphonamides on ditch-plates made of laked horse-blood agar as recommended by Harper and Cawston (1945), the ditch containing 1 in 5,000 sulphathiazole. All ditch-plates, whether for testing penicillin, streptomycin, or sulphonamide sensitivity, were kept for 24 hours before use to allow diffusion of the chemotherapeutic agent, and part of every ditch-plate was seeded with the Oxford staphylococcus as a control. Phage-typing of all strains was carried out by the method now used at the Central Public Health Laboratory, using the same 25 filtrates. The method is based on the work of Wilson and Atkinson (1945).

Penicillin Sensitivity

Specimens were examined from 100 consecutive patients with infection due to coagulase-positive staphylococci (hereafter referred to as *Staph. pyogenes*). The results are given in Table I, in-patients and out-patients being separated. From 35 patients penicillin-resistant strains of *Staph. pyogenes* were isolated: from 24, all colonies tested were resistant to penicillin; from 11, sensitive and resistant colonies were isolated in each case from a single specimen. Thus 111 strains of *Staph. pyogenes* were obtained from 100 specimens. The difference between sensitive and resistant strains was clear-cut in every instance. All the penicillin-resistant colonies when streaked across the penicillin

ditch-plates grew at least to the ditch, whereas the sensitive colonies showed an area of inhibition similar to that shown by the Oxford staphylococcus. It will be seen from Table I that the incidence of resistant strains was greater in in-patients than in out-patients. The results, analysed according to type of infection, are shown in Table II.

TABLE II.—Results According to Type of Infection

Type of Infection	Total Patients	Patients Yielding Resistant Strains
Carbuncles, abscesses, boils, etc.	53	14
Superficial skin lesions	19	9
Infected wounds	5	3
Pulmonary	8	4
Conjunctival	4	2
Aural	1	—
Nasopharyngeal	4	—
Genito-urinary	5	3
Inadequate information	1	—
	100	35

Previous treatment with penicillin was studied to see if this had any relation to the incidence of resistant strains. In only 67 of the patients was information regarding penicillin treatment available. Penicillin sensitivity in relation to treatment within the preceding three months in this group is shown in Table III.

TABLE III.—Relation of Previous Treatment to Incidence of Resistant Strains

	Penicillin Treatment within Previous 3 Months	No Penicillin Before Specimen Taken
Penicillin-sensitive strains only isolated	19	22
Penicillin-resistant strains isolated	22	8
Penicillin-sensitive and penicillin-resistant strains isolated	3	6

It will be seen that 22 of 41 patients who had been treated with penicillin yielded penicillin-resistant staphylococci, whereas only eight of 30 patients not treated with penicillin yielded such strains. One patient with an axillary abscess had a specimen taken before receiving any penicillin, and this yielded a very few colonies of penicillin-resistant and a heavy growth of penicillin-sensitive *Staph. pyogenes*. Treatment with penicillin was then started, and three weeks later a specimen of pus was received which yielded a heavy growth of *Staph. pyogenes*, and all colonies tested were penicillin-resistant.

The incidence of penicillin-resistant strains was correlated with length of hospital treatment in 46 cases, and the figures are given in Table IV. It will be seen that only

TABLE IV.—Incidence of Penicillin-resistant Strains of *Staph. Pyogenes* in Relation to Length of Treatment in this Hospital

No. of Days under Treatment	Patients Yielding			Total
	Penicillin-sensitive Colonies Only	Penicillin-resistant Colonies Only	Sensitive and Resistant Colonies	
0	14 (4)	2 (1)	1 (1)	17 (6)
1-7	4 (2)	1	0	5 (2)
8-14	3 (3)	1	2	6 (3)
15-28	3 (1)	7 (1)	0	10 (2)
Over 28	5 (5)	3 (1)	0	8 (6)
Total	29 (15)	14 (3)	3 (1)	46 (19)

The figures in parentheses refer to the number of out-patients in each group.

4 out of 22 patients who had been attending the hospital for a week or less yielded penicillin-resistant strains, whereas 10 of 18 patients who had been attending for a fortnight or more yielded such organisms.

TABLE I.—Analysis of Patients Yielding *Staph. Pyogenes* in Relation to Penicillin Sensitivity

Aug.-Dec., 1948	No. of Patients	Patients with Penicillin-resistant Strains		
		All Colonies Resistant	Sensitive and Resistant Colonies Isolated	Total
In-patients	49	13	7	20
Out-patients	51	11	4	15
Total	100	24	11	35

Degree and Type of Resistance to Penicillin

All 35 penicillin-resistant strains destroyed penicillin. As is now well recognized (Luria, 1946; Barber, 1947a) the degree of resistance of such organisms when measured in the laboratory may vary many hundredfold according to the size of inoculum used. It is therefore extremely difficult to devise a test giving accurate information on the degree of resistance which will help the clinician in deciding the probable effect of penicillin in a particular case of infection. Gilson and Parker (1948) have suggested that the double sensitivity test in broth, using two different-sized inocula, is the most informative, as the results obtained are directly related to the degree and rate of penicillinase production. This test was carried out on 17 of the resistant strains of *Staph. pyogenes* isolated in this series (Table V). It will be seen that a large inoculum was

TABLE V.—Showing Degree of Resistance

Greatest Concentration of Penicillin Permitting Growth		No. of Strains
Large Inoculum (Approx. 1,000,000 orgs.)	Small Inoculum (Approx. 1,000 orgs.)	
50 u./ml. or more	1-4 u./ml.	7
50 " " " " " " " "	0.25-0.5 u./ml.	5
25 " " " " " " " "	1 u./ml.	1
25 " " " " " " " "	0.25-0.5 u./ml.	2
12.5 " " " " " " " "	0.25 u./ml.	1
12.5 " " " " " " " "	0.03 u./ml.	1
0.03 " " " " " " " "	0.03 u./ml.	Oxford Staphylococcus

able to grow in from 12.5 to 50 units per ml., whereas a small inoculum was able to grow only in from 0.03 to 4 units per ml.

Phage-typing

All the 111 strains of *Staph. pyogenes* were phage-typed, and the results in relation to penicillin sensitivity are given in Table VI. Cultures reacting with one or more closely

TABLE VI.—Phage Groups of 111 Strains of *Staph. Pyogenes* Isolated in Present Series

Phage Group	No. of Strains of <i>Staph. pyogenes</i>	
	Penicillin-sensitive	Penicillin-resistant
6/7/47	9	24
52A	18	4
3	16	0
42	5	0
29/31/52	6	0
44	1	0
Non-typable	21	7
Total	76	35

related phages have been grouped together, and the strains in a particular group do not all give identical reactions. Of those classified as 6/7/47 nearly all reacted strongly with phage 47, and many also reacted with various combinations of 6, 7, and 3298. A few strains included in this group were sensitive to phage 6 or phage 7 only. Group 29/31/52, again, consists of strains showing varying reactions with one or more of these three phages. Nearly all the strains classified as 3 were sensitive to only one of the phages 3A, 3B, and 3C, and similarly strains in the 42 group reacted only with one of the phages 42B, 42C, 42D, and 42E. Apart from trace reactions, the 52A strains reacted with this phage alone. The non-typable group consists mainly of strains giving no reactions, but includes a few which were very sensitive and could not be classified.

It will be seen from Table VI that of the 35 penicillin-resistant strains as many as 24 fell into the 6/7/47 group, and that the only other typable strains belong to type 52A.

The penicillin-sensitive strains, on the other hand, were distributed among all the groups, only nine out of 76 belonging to group 6/7/47.

As mentioned above, penicillin-sensitive and penicillin-resistant strains were isolated from the same patient in 11 cases. These 11 pairs of strains were phage-typed and the results are given in Table VII. In nine of the 11 pairs the

TABLE VII.—Phage Types of Pairs of Strains Isolated from the Same Patient

Patient	Phage Type of Strain of <i>Staph. pyogenes</i>	
	Penicillin-sensitive	Penicillin-resistant
5	N.T.	6*
10	47*	N.T.
12	N.T.	N.T.
32	42E	47*
40	N.T.	47*
41	N.T.	7*
46	N.T.	52A
63	52A	6/47*
75	N.T.	6/47*
82	52A	52A
92	42E	N.T.

N.T. = Non-typable. * Side-reactions.

two appear to be different in phage-type, but it is unfortunate that in eight cases one of the pair is non-typable. From one of these 11 patients penicillin-resistant and penicillin-sensitive strains of *Staph. pyogenes* were isolated from both the lesion (sycosis barbae) and the nose. From each site the penicillin-resistant strain was phage type 6/47 and the penicillin-sensitive strain non-typable.

It occurred to us that the apparent correlation of penicillin resistance and phage group 6/7/47 might be a purely local phenomenon. A number of penicillinase-producing strains of *Staph. pyogenes* isolated from patients in widely separated hospitals were therefore collected together and phage-typed. The cultures from Hammersmith Hospital and the General Lying-In Hospital, S.E.1, were already in our possession, and the cultures from Canterbury, Manchester, and the West London Hospital were kindly sent by Dr. Forbes, Dr. Martyn, and Dr. Morris respectively. Except for the cultures from Manchester, which were isolated from healthy infants, all strains came from cases of infection. The results are given in Table VIII.

TABLE VIII.—Phage Types of Penicillin-resistant Strains of *Staph. Pyogenes* Isolated from Patients

Phage Group	Source						Total
	Hammer-smith Hospital	St. Thomas's Hospital	General Lying-in Hospital, S.E.1	West London Hospital	Kent and Canterbury Hospital	St. Mary's Hospital, Manchester	
6/7/47	25	27	0	1	27	5	85
52A	1	4	15	0	1	0	21
42	3	0	0	0	0	0	3
3	1	0	0	0	0	0	1
29/31/52	1	0	0	0	0	0	1
N.T.	3	8	13	0	4	1	29
Total	34	39	28	1	32	6	140

In all, 140 strains were tested and as many as 85 (61%) fell into the 6/7/47 group. Apart from non-typable strains the only other large group is 52A. This is mainly due to an outbreak of infection among the babies at the General Lying-In Hospital which at the time of writing is under investigation. Nearly all the infections occurring at present in this maternity hospital are due to penicillinase-producing *Staph. pyogenes* and, as will be seen in the table, most of the strains are phage type 52A. A very large number of nurses in the hospital are carrying a similar organism in the nose.

Streptomycin and Sulphonamide Sensitivity

All 111 strains were tested for sensitivity to streptomycin and sulphonamides. The results are presented in relation to penicillin sensitivity in Table IX. All strains showed a

TABLE IX.—*Streptomycin and Sulphathiazole Sensitivity of 111 Strains of Staph. Pyogenes*

	Penicillin-sensitive	Penicillin-resistant	Total
Streptomycin-sensitive ..	76	35	111
Streptomycin-resistant ..	0	0	0
Sulphathiazole-sensitive ..	72	18	90
Sulphathiazole-resistant ..	4	17	21

sensitivity to streptomycin comparable to that of the Oxford staphylococcus. One of the patients, who had a lung abscess infected with penicillin-resistant *Staph. pyogenes*, *Proteus*, and non-haemolytic streptococci, was subsequently treated with streptomycin. Within five days the *Staph. pyogenes* had become highly resistant to this antibiotic.

Twenty-one of the 111 strains were considerably more resistant to sulphathiazole than the Oxford staphylococcus, and 19 of these strains grew at least to the edge of the ditch containing 1 in 5,000 sulphathiazole. It is interesting that 17 of the 21 sulphathiazole-resistant strains were also penicillin-resistant. Eight of the patients yielding sulphonamide-resistant strains had had some form of sulphonamide treatment before the specimen was taken, eight had not, and from five information in relation to treatment is not available.

 α -Toxin Production

The strains isolated in the present series were all coagulase-positive on testing by the slide method. As Schwabacher, Cunliffe, Williams, and Harper (1945) and Christie, North, and Parkin (1946) have suggested that the production of α -lysin is more closely correlated with pathogenicity than coagulase production, all the strains were examined for α -toxin production, using the sheep-blood plate method of Gillespie and Simpson (1948). Of the 111 strains, 101 were α -toxigenic, two were negative, and eight were regarded as giving doubtful reactions. The negative and doubtful strains were tested for coagulase by the tube method of Fisk (1940) and found to be positive. The doubtful reactions on the sheep-blood agar plates were due in some instances to the simultaneous production of β -toxin in amounts sufficient to mask the appearances due to the α -toxin. On testing the eight doubtful strains for the production of α -toxin in broth, using the method of McFarlan (1938), four were found to be positive, while the remaining four were negative, as also were the two strains found to be negative by the sheep-blood plate method. Thus of the 111 coagulase-positive strains 105 were α -toxigenic.

Of the non-toxigenic strains, three belonged to phage type 3C; the remainder were non-typable.

Discussion

It is remarkable that such a high proportion of penicillin-resistant strains of *Staph. pyogenes*, isolated from patients in widely different hospitals, should belong to phage group 6/7/47. While in the present state of our knowledge it is possible only to speculate on the meaning of this, it may well be of considerable epidemiological importance. It is possible that strains of phage group 6/7/47 are genetically less stable than those of other phage groups, and have thus given rise to penicillin-resistant mutants more readily. A significant number of the remaining penicillin-resistant strains were type 52A, but nearly all these were isolated from neonatal infections occurring in a single maternity

hospital over a period of three months. It is interesting that *Staph. pyogenes* of phage type 52A has been isolated from the noses of many nurses in this maternity hospital, and that some of the strains are sensitive to penicillin whereas others are resistant. It is possible that an originally sensitive strain of *Staph. pyogenes* carried in this hospital has recently given rise to a penicillin-resistant mutant which has now established itself there.

The ultimate origin of penicillin-destroying strains of *Staph. pyogenes* is still undecided. Spink and Ferris (1947) favour the hypothesis that such strains arise as mutants from penicillin-sensitive organisms. The work of Barber (1949) on the readiness with which, *in vitro*, penicillinase-producing staphylococci give rise to penicillin-sensitive variants supports this theory. Penicillin-destroying mutants, however, cannot be induced by growing penicillin-sensitive strains of *Staph. pyogenes* in penicillin *in vitro*. Spink *et al.* (1945, 1947) claim that such a change may be induced *in vivo* by penicillin treatment. As, however, their strains of *Staph. pyogenes* were not typed, it is possible that they were dealing with mixed infections due to penicillin-sensitive and penicillin-resistant strains of different types; that the latter, initially in the minority, were favoured at the expense of the former, and thus by a simple process of selection ultimately supplanted the penicillin-sensitive organisms.

Such mixtures of penicillin-sensitive and penicillin-resistant strains of *Staph. pyogenes* have now been isolated from the same patient on many occasions, and in most cases where such pairs have been phage-typed they have been found to give different reactions. Of 11 such pairs in the present series nine gave different phage reactions, and it seems likely that they were different phage types, although it is impossible to be quite certain of this where one of the pair was non-typable. In previous studies (Barber, 1947a, 1947b; Barber and Rozwadowska-Dowzenko, 1948) 10 such pairs were phage-typed and eight pairs were shown to be of different types.

Whatever the ultimate origin of penicillin-destroying strains of *Staph. pyogenes*, it seems likely (Barber and Rozwadowska-Dowzenko, 1948) that selection plays a large part in the increasing incidence of such strains in hospitals. The work of Harley *et al.* (1946) and Forbes (1949) further makes it clear that the incidence of penicillin-resistant strains isolated from staphylococcal infections in hospital in-patients is much greater than that in out-patients. In the present study it will be seen that 20 of 49 in-patients yielded penicillin-resistant strains compared with 15 of 51 out-patients, and that there was a significantly higher incidence of penicillin-resistant organisms in patients who had been under hospital treatment for more than a fortnight.

Kirby (1944) first pointed out that penicillin-resistant strains of *Staph. pyogenes* isolated from infective processes were characterized by the production of a powerful penicillin-inactivator. Since then Spink, Hall, and Ferris (1945), Bondi and Dietz (1945), Gots (1945), Barber (1947a, 1947b), Barber and Rozwadowska-Dowzenko (1948), Martin and Whitehead (1949), Martyn (1949), and Forbes (1949) have recorded studies in which all penicillin-resistant strains of *Staph. pyogenes* isolated from cases of infection or human carriers were shown to destroy penicillin. The resistant strains isolated in the present series likewise have this property.

Luria (1946) and Barber (1947a) have both shown that the degree of resistance of penicillinase-producing organisms recorded in the laboratory was dependent on the size of inoculum used. In the present series it will be seen (Table V) that with many strains a small inoculum was

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 α -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 α -toxigenic. Although no evidence could be obtained to indicate that the α -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 α -toxigenic.

We are grateful to Dr. R. E. O. Williams and the staff of the Staphylococcal Reference Laboratory for teaching us to phage-type staphylococci and for supplying us with a set of filtrates. We should also like to thank Dr. J. Bamforth and the staff of the Jenner Laboratory for supplying us with the specimens on which this work was based, Dr. Bhatia for assistance with some of the penicillin-sensitivity tests, and Dr. Forbes, Dr. Martyn, and Dr. Morris for sending us cultures of penicillin-resistant *Staph. pyogenes*.

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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