

doses, and partly because of the biological variability in the radiosensitivity of different glands. With his method thyrotoxic patients can be treated safely and effectively without elaborate techniques. Though we do not allow for the percentage uptake of ^{131}I by the gland in deciding on the dose to be given, we consider preliminary tracer investigations desirable to confirm the diagnosis.

Pre-treatment of thyrotoxic cases with methylthiouracil and thyroxine before giving ^{131}I has been used by Fraser *et al.* (1954) to produce a more uniform uptake of the isotope by the gland. We investigated the effects of pre-treatment with methylthiouracil on the results of ^{131}I therapy. A series of 28 cases treated with methylthiouracil until one week before the ^{131}I was administered provided a significantly smaller number of one-dose cures (28%) than a comparable series which received no premedication (75%). Further investigations have shown that this effect is probably due to an increased degree of resistance to radiation conferred on the gland by the pre-treatment. This factor must be taken into account whatever scheme of dosage is used, and further observations suggest that a dose at least 25% larger must be given to those who have recently received methylthiouracil.

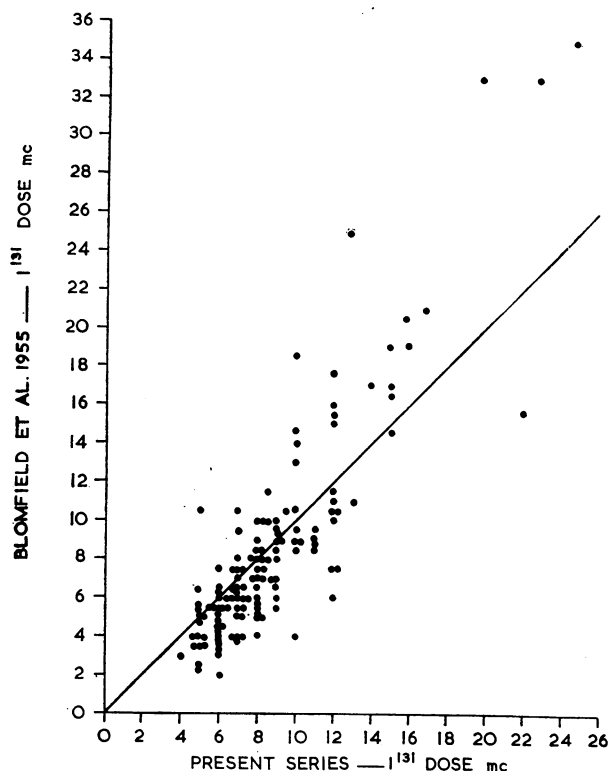


Fig. 8.—Therapeutic doses of ^{131}I , prescribed in the present series, plotted against doses calculated from the formula of Blomfield *et al.* (1955). The oblique line has been drawn at 45 degrees to the ordinates.

Choice of Treatment

No hard-and-fast rules can be laid down, but the clinician will show wisdom if he takes advantage of ^{131}I treatment when it is available and uses it to treat patients whose disease has recurred after operation and those with heart disease. It is of course much the most pleasant form of treatment, and if I were to become thyrotoxic it is the form I would choose. Younger patients are usually best treated in the first instance

with a course of an antithyroid drug such as potassium perchlorate. Those who relapse should be advised to have a thyroidectomy after they have been rendered euthyroid by a further course of an antithyroid drug.

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[The Second Lecture will be published next week, with the list of references.]

REVERSAL OF ANTIBIOTIC RESISTANCE IN HOSPITAL STAPHYLOCOCCAL INFECTION

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There is much evidence to suggest that some at any rate of the multiple-resistant strains of *Staph. pyogenes* so prevalent in our hospitals to-day are of enhanced virulence, both in their capacity to initiate infection and in the severity of the infection produced. Thus, although such strains are relatively uncommon among staff carriers, they are responsible for the majority of cases of post-operative infection (Alder *et al.*, 1955; Barber and Burston, 1955; Shooter *et al.*, 1958), and some investigators have reported that infection with "hospital staphylococci" may be of unusual severity (Rountree and Freeman, 1955; Beaven and Burry, 1956; Ede *et al.*, 1959). While it cannot be assumed from this that multiple resistance and enhanced virulence are necessarily associated, the process of selection of drug-resistant staphylococci in hospitals may have tended to select strains of high virulence. In fact, nearly all the multiple resistant staphylococcal infections in hospitals to-day are due to a relatively few strains of *Staph. pyogenes* most of which belong to phage group III or type 80.

The principles for preventing hospital cross-infection enunciated long before the introduction of antibiotics remain the same to-day, but the ubiquity of the staphylococcus makes their strict application difficult in relation to this microbe. It is possible that pathogenic staphylococci could be kept at bay if we had sufficient isolation facilities, but at present this is not the case in most hospitals in Britain.

It seemed reasonable, therefore, to attempt to break the vicious circle by introducing a controlled antibiotic policy, designed to inhibit the emergence of drug-resistant staphylococci and to favour penicillin-sensitive strains. The present investigation was undertaken to

*Working with a grant from the Medical Research Council.

study the effect of such a policy, in association with the strict application of a number of anti-cross-infection measures introduced six months prior to the antibiotic policy.

Scope of Investigation

The incidence and drug-resistance of all staphylococcal infections in the surgical wards of a large general hospital have been studied over the period October 1, 1957, to June 30, 1959. Seven wards were involved in the study: two female and two male general surgical wards, one female and one male ward primarily devoted to orthopaedic patients, and one male urological ward. The ward units consist of open wards with 15 to 24 beds, plus one to three side-wards. During the course of the investigation a total of 5,239 patients were admitted.

Anti-Cross-Infection Measures

A cross-infection committee was set up in the hospital in April, 1957, and in the ensuing six months a number of measures were introduced to reduce hospital cross-infection. The most important of these were as follows:

1. *Isolation*, wherever possible, and barrier-nursing of patients with multiple-resistant staphylococcal infection. As a policy this was only partially effective for two reasons. Firstly, isolation was not instituted for at least 24-48 hours after the onset of infection, since the criterion depended on a bacteriological report. Secondly, since the number of side-wards was small one was not always available. For this reason isolation of all patients with infections, whatever the antibiotic sensitivity, was quite impracticable.

2. *Laundry Procedures*.—All sorting of dirty linen in wards was abandoned. The laundering of blankets between patients was instituted and all blankets were treated with a quaternary ammonium compound in the rinse. Frequent laundering of curtains, which surround most of the beds, was recommended, and these also were treated with a quaternary ammonium compound.

3. *Hospital Sterilization*.—All autoclaves and their use were thoroughly checked and where necessary improvements introduced.

4. *Ward and Theatre Hygiene*.—Attempts were made by means of discussions, lectures, and general propaganda to keep ward and theatre hygiene at a high level.

5. *Ward Closure*.—On two occasions during the investigation a ward was closed because of an outbreak of staphylococcal infection.

Antibiotic Policy

The essential features of the antibiotic policy were restriction in the use of all antibiotics for prophylactic purposes, strict limitation of the use of penicillin, and the general employment of double chemotherapy, each drug being given in full dosage. A total ban on penicillin was clearly impossible, since it is the antibiotic of choice for a number of infections. Its use was therefore confined to two medical and two surgical wards, and the nursing staff of these wards were supplied with cartridge syringes and taught to give injections of penicillin without spraying penicillin into the atmosphere (cf. Gould, 1958).

The policy was put into operation at the beginning of April, 1958, and all medical officers were individually circulated with the following instructions:

1. *General Restriction in Use of All Antibiotics*.—In particular the following only to be used where there is definite indication that they are likely to be of benefit to the patient: penicillin, streptomycin, tetracyclines (chlorotetracycline, oxytetracycline, and tetracycline), chloramphenicol, erythromycin, and novobiocin.

2. *Abandonment of Penicillin*, except in the following wards: B5, B6, C3, C4. (Wards B5 and B6 are medical wards and are not referred to in this study. Wards C3 and C4 are the two wards devoted primarily to orthopaedic cases.) Where an exception to this rule is made, patient must be in a *side-ward*. All penicillin injections to be given with special precaution to prevent aerial contamination.

3. *Use of the Chemotherapeutic Agents in Combination*, wherever possible, and always when one of the antibiotics listed in paragraph 1 is being used.

4. Local application to be carried out only with preparations not suitable for systemic administration—for example, neomycin, bacitracin, polymyxin, chlorhexidine.

During the course of the investigation cross-resistance between chloramphenicol and erythromycin was noted (cf. Barber *et al.*, 1958), and in January, 1959, the following was added to item 3: *Combination of Chloramphenicol and Erythromycin should be avoided*.

A list of conditions for which penicillin was the drug of choice was appended, together with the following recommendations of suitable combinations for the types of infection most frequently encountered in the hospital:

I. MEDICAL WARDS

Respiratory Infections

Acute pneumonia: Sulphonamides, if necessary with chloramphenicol, or tetracycline, subject to bacteriological findings.

Chronic bronchitis: Combinations of tetracycline, sulphonamides, and chloramphenicol; *neomycin inhalation*.

Intestinal Infections:

Bacillary dysentery: Sulphonamides, polymyxin.

Salmonella infections: Chloramphenicol and sulphonamides.

Amoebiasis: Oxytetracycline.

Diverticulitis: Sulphonamides, when necessary.

Meningitis { Meningococcal: Sulphonamides.
H. influenzae: Chloramphenicol and streptomycin.

Brucellosis: Tetracycline and streptomycin.

Urinary Infections: Pyelitis, pyelonephritis, cystitis, etc., dependent on bacteriology, including sensitivity tests.

Skin Infections: Topical application of neomycin, bacitracin, polymyxin, chlorhexidine, in various combinations.

Lymphogranuloma: Sulphonamides and tetracycline.

II. SURGICAL WARDS

A. *Prophylaxis*: No antibiotics except for the following:

For Chest: None, unless purulent bronchitis present at time of operation; if so, tetracycline and chloramphenicol.

Cardiac Surgery (arterial grafts, etc.): Penicillin, streptomycin, and chloramphenicol for four days.

Insertion of Foreign Bodies (e.g., bone grafts, etc., hernias): As for cardiac surgery.

Compound Fractures: Chlorotetracycline and chloramphenicol.

Craniotomy and Laminectomy: Sulphonamides and chloramphenicol. Possibility of sprays in local application to be investigated.

Burns: Local application of neomycin and polymyxin with bacitracin or chlorhexidine. Very extensive burns: systemic tetracycline and erythromycin.

Skin Grafts: No antibiotic cover if clean.

Bowel Surgery: Neomycin-bacitracin capsules or phthalylsulphathiazole and neomycin.

B. *Treatment*. *Peritonitis* (e.g., with burst appendix, infected gall-bladder, pancreatitis, etc.): Tetracycline and either erythromycin or novobiocin, pending bacteriological investigation.

Paediatrics

Neonatal: Staphylococcal infection, erythromycin and novobiocin, subject to bacteriological reports. Local treatment with neomycin and bacitracin, or sulphacetamide in eye infections with staphylococci.

Older Children: *Acute respiratory infections*: Tetracycline and sulphonamides.

Changes in Antibiotic Consumption Following the Antibiotic Policy

Comparison of the figures for consumption of antibiotics in the hospital in the year April, 1957, to March, 1958, and those in the year April, 1958, to March, 1959, has shown that after the introduction of the antibiotic policy the following changes in consumption occurred: penicillin, +2.6; tetracycline, ×1.8; chloramphenicol, ×2.0; erythromycin, ×2.5; novobiocin, ×6.

Bacteriological Investigations

Ward sisters, house officers, and registrars were encouraged to take swabs and send specimens of sputa, etc., for bacteriological examination wherever there was the least suspicion of sepsis. The specimens were initially plated out on plain blood-agar plates and usually on two or more antibiotic ditch-plates. When staphylococci were isolated they were tested for coagulase by the slide test, and coagulase-positive strains were tested for sensitivity to penicillin, streptomycin, tetracycline, chloramphenicol, erythromycin, novobiocin, and vancomycin. A single colony and a mixed streak from each strain were tested on ditch-plates. The concentrations of antibiotic in the ditch were as follows: penicillin 10 units/ml., chloramphenicol 50 µg./ml., vancomycin 100 µg./ml., all other antibiotics 25 µg./ml. The Oxford staphylococcus was streaked across the centre of each ditch. Strains were recorded as resistant if they grew to the edge of the ditch or right across it, and partially resistant if they grew nearer to the ditch than the Oxford staphylococcus but not to the edge. Except with streptomycin and erythromycin, strains showing partial resistance were uncommon and for the purposes of analysis have been included with resistant strains.

Nasal swabs were also taken from many patients and members of the staff, and these were initially plated on phenolphthalein phosphate nutrient agar (Barber and Kuper, 1951). Subsequent treatment of phosphatase-positive colonies was similar to that described above.

After January 1, 1958, all strains of *Staph. pyogenes* from infective processes and a proportion of those

isolated from nasal carriers were bacteriophage-typed by the method of Williams and Rippon (1952).

Incidence and Drug-Resistance of Staphylococcal Infection

The incidence and drug-resistance of staphylococcal infection in the surgical wards between October 1, 1957, and June 30, 1959, have been analysed quarterly and the results are given in Table I and Figs. 1 and 2. Most of the anti-cross-infection measures were introduced before or during the first quarter. The antibiotic policy was introduced at the beginning of the third quarter.

TABLE I.—*Staphylococcal Infection in Surgical Wards, October 1, 1957, to June 30, 1959*

Date	No. of Patients Admitted	Infections								
		Total	Pen. S.*		Pen. R. Tet. S.		Pen. R. Tet. R.		Eryth. R.†	
			No.	%	No.	%	No.	%	No.	%
Oct.-Dec., '57	728	76	9	12	14	18	53	70	8	11
Jan.-Mar., '58	722	83	22	26	19	23	42	51	5	7
Apl.-June, '58	812	74	15	20	18	24	41	56	10	14
July-Sept., '58	783	53	18	34	12	23	23	43	10	19
Oct.-Dec., '58	708	50	19	38	12	24	19	38	10	20
Jan.-Mar., '59	746	58	21	36	12	21	25	43	17‡	29
Apl.-June, '59	740	58	28	48	9	16	21	36	6	10
	5,239	452	132	—	96	—	224	—	66	—

* All but five of these infections were also sensitive to tetracycline and all were sensitive to erythromycin.

† All but one of these infections were also resistant to penicillin and tetracycline.

‡ 11 of these infections were of similar phage type and occurred in a single ward.

All infections have been recorded, however slight, and both wound and chest infections have been included.

It will be seen that during the 21-month period 5,239 patients were admitted to the wards, and 452 (9%) of them had a staphylococcal infection. The total incidence of infections per patient dropped from 10% to 7% between the second and fourth quarters, since when it has remained fairly stable.

The drug-sensitivity of the infection, on the other hand, has changed steadily throughout the period of study. At the beginning of the investigation 70% of the infections were resistant to penicillin and tetracycline

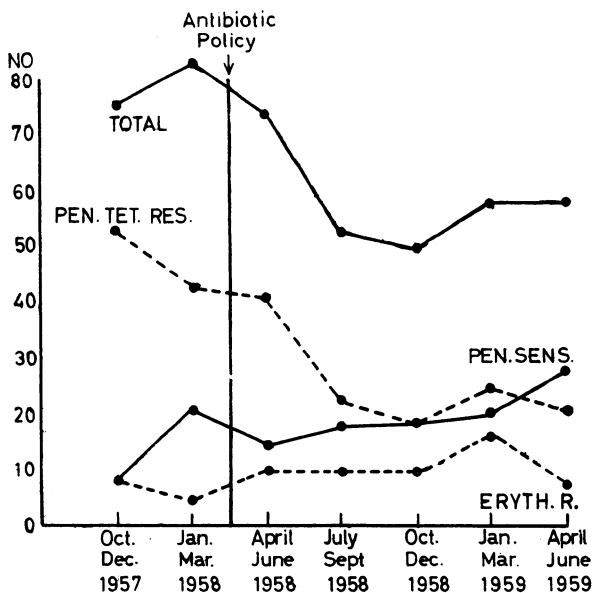


FIG. 1.—Number of staphylococcal infections with various antibiotic-sensitivity patterns.

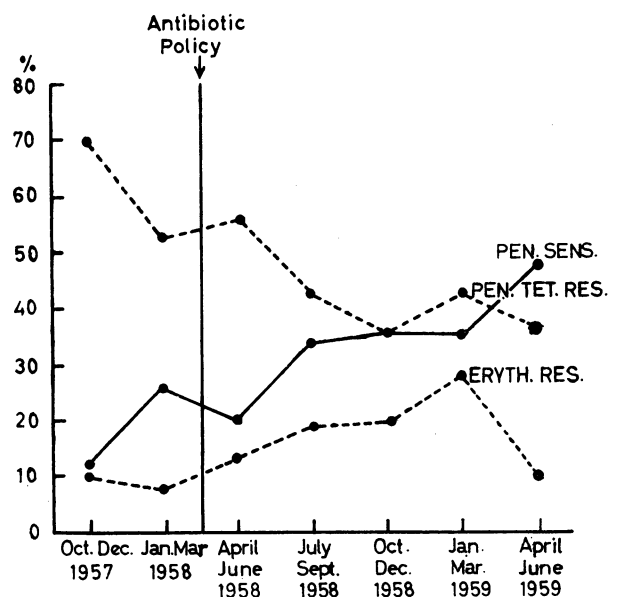


FIG. 2.—Percentage of staphylococcal infections with various antibiotic-sensitivity patterns.

and only 12% were sensitive to all antibiotics tested, including penicillin. In the last quarter the incidence of infection resistant to penicillin and tetracycline had dropped to 36% and that of penicillin-sensitive infection had risen to 48%.

In the last quarter, four of the penicillin-sensitive strains were resistant to tetracycline; only one such strain had been isolated in the previous 18 months. All the penicillin-sensitive strains were also sensitive to streptomycin, erythromycin, and novobiocin, but two, both isolated in the last quarter, were resistant to chloramphenicol.

Most of the penicillin- and tetracycline-resistant infections were also resistant to streptomycin, but 29 of the 224 were sensitive to this antibiotic. As many as 66 of these infections were also resistant to erythromycin. It will be seen from Table I that the erythromycin-resistant infections occurred throughout the period of investigation and that there was no significant change in incidence. The high figure in the sixth quarter, January–March, 1959, was due to an outbreak of infection in which 11 patients in one of the six wards became infected by a single strain of *Staph. pyogenes*.

Chloramphenicol resistance is not recorded in the table, but there were 40 such infections scattered throughout the period of investigation. In 27 instances this was associated with erythromycin resistance, and these 27 infections were in fact resistant to penicillin, streptomycin, tetracycline, chloramphenicol, and erythromycin.

Only one infection resistant to novobiocin was encountered, and none of the infections was resistant to vancomycin.

Generalized and Fatal Infections

Most of the infections recorded were localized to a single site and many were of very little clinical significance. In 49 patients, however, the infection was generalized; 24 of these patients died, and though infection was not usually the sole cause of death it was in every case a major contributory factor. As many as 44 of the generalized infections were resistant to penicillin and tetracycline, and 16 of these were also resistant to erythromycin. All but four of the strains were tested for bacteriophage sensitivity; 11, including six from fatal cases, were phage type 80; the remainder were of various types, all belonging to group III.

Table II shows that 12 of the patients with generalized infection were infected before admission. All these were suffering from renal failure and had been transferred from other hospitals for treatment on the artificial kidney. These patients, all of whom were

TABLE II.—Incidence and Mortality of Generalized Staphylococcal Infection

	Patients Infected			
	Before Admission		In Hospital	
	No.	Deaths	No.	Deaths
October–December, 1957 ..	0	0	14	6
January–March, 1958 ..	2	2	7	5
April–June, 1958 ..	1	1	6	2
July–September, 1958 ..	3	2	3	0
October–December, 1958 ..	2	2	2	2
January–March, 1959 ..	1	0	4	2
April–June, 1959 ..	3	0	1	0
	12	7	37	17

admitted with infection due to multiple-resistant strains of staphylococci from other hospitals, constituted a major problem in attempting to eradicate such organisms from the hospital being studied. It will also be seen from Table II that the incidence of generalized infection contracted in the hospital has fallen with the fall in the incidence of multiple-resistant infection.

Strains of *Staph. pyogenes* Responsible for Infection

From January, 1958, the strains of *Staph. pyogenes* isolated from infections in the surgical wards were all tested for sensitivity to bacteriophage. When it was found that two or more infections in a single ward were due to staphylococci with a similar antibiotic-sensitivity pattern and of the same bacteriophage type, it was assumed that a single strain of *Staph. pyogenes* was responsible for all the infections. The wards were taken as separate units because they tended to have staphylococci of different types. On this basis the incidence and drug-resistance of the strains of *Staph. pyogenes* responsible for the infections in the hospital were analysed, and the results are summarized in Table III and Figs. 3 and 4.

It will be seen that following the introduction of the antibiotic policy at the beginning of April, 1958, the percentage of strains sensitive to penicillin rose from 28 to 54. In contrast to this the percentage of strains resistant to penicillin alone fell from 28 to 17; and the percentage of strains resistant to penicillin and tetracycline fell from 44 to 29. The incidence of strains resistant to erythromycin rose to begin with and then fell. This may have been due to the frequent use of

TABLE III.—Strains of *Staph. pyogenes* Responsible for Infections in Surgical Wards, January, 1958, to June, 1959

Date	Total	Infections							
		Pen. S.*		Pen. R. Tet. S.		Pen. R. Tet. R.		Eryth. R.†	
		No.	%	No.	%	No.	%	No.	%
Jan.–Mar., '58 ..	61	20	33	19	31	22	35	4	7
Apr.–June, '58 ..	50	14	28	14	28	22	44	6	12
July–Sept., '58 ..	43	13	30	11	26	19	44	9	21
Oct.–Dec., '58 ..	35	15	43	10	29	10	29	7	20
Jan.–Mar., '59 ..	38	19	50	10	25	9	24	4	10
Apr.–June, '59 ..	48	26	54	8	17	14	29	4	8

* All but three of these strains were also sensitive to tetracycline.

† All but one of these strains were also resistant to penicillin and tetracycline.

chloramphenicol and erythromycin in combination until January, 1959, when attention was drawn to the fact that there was cross-resistance between these two antibiotics (Barber *et al.*, 1958).

Virulence of Multiple Resistant Strains of *Staph. pyogenes*

During the course of this study 452 staphylococcal infections were encountered and strains from 369 of these were typed by bacteriophage sensitivity. From this fairly extensive material an attempt has been made to assess the virulence of strains of different antibiotic sensitivity patterns. To determine whether certain types of staphylococci were more likely to initiate infection the number of strains (based on bacteriophage typing) of a given antibiotic sensitivity were compared with the number of such infections, and from this the incidence of infection per strain was calculated. The results are given in Table IV, from which it will be seen that with

antibiotic-sensitive strains and strains resistant to penicillin only the incidence was 1.4, whereas with strains resistant to penicillin and tetracycline it was 2.0, and with strains resistant to these two antibiotics and erythromycin it was 3.0. It does not, of course, follow from this that all multiple-resistant strains were more likely to initiate infection than were antibiotic-sensitive staphylococci. Actually the results reflect the fact that a few of the multiple-resistant strains were each responsible for a large number of infections. On the other hand, none

TABLE IV.—Incidence of Infections Caused by Strains of *Staph. pyogenes* of Different Antibiotic Sensitivities

Antibiotic Sensitivity of Infecting Strain			No. of Strains	No. of Infections	Incidence of Infections per Strain
Pen.	Tet.	Eryth.			
S	S	S	85	116	1.4
R	S	S	57	82	1.4
R	R	S	59	119	2.0
R	R	R	17	52	3.0

TABLE V.—Relation of Antibiotic Sensitivity to Incidence of Generalized Infection

Antibiotic Sensitivity of Infecting Strain			Total No. of Infections	Generalized Infections		
Pen.	Tet.	Eryth.		No.	Percentage of Total	No. of Deaths
S	S	S	132	3	2.3	1
R	S	S	96	2	2.0	0
R	R	S	158	28	17.7	14
R	R	R	66	16	24.2	9

of the strains sensitive to all antibiotics tested or resistant to penicillin only was responsible for more than two infections.

In an attempt to assess the severity of infection caused by strains of different antibiotic-sensitivity pattern, the incidence of generalized infection was studied. From Table V it will be seen that only 3 out of 132 antibiotic-sensitive infections and only 2 out of 96 infections resistant to penicillin only were generalized. Only one

patient in these two groups died, and he was 85 years old. On the other hand, as many as 28 of 158 infections resistant to penicillin and tetracycline and 16 out of 66 infections resistant to these two plus erythromycin became generalized, and 23 of these patients died.

Nasal Carriers

Nurses.—A survey of nasal carriers among the entire nursing staff was undertaken six times during the 21 months. The results are given in Table VI. It will be noted that on each occasion approximately half the nurses tested carried *Staph. pyogenes* and that the majority of carriers carried strains resistant to penicillin but sensitive to tetracycline. The percentage of carriers carrying penicillin-sensitive strains increased from 24 to 37 between July and November, 1958, and thereafter remained at the higher level. The incidence of nurses carrying multiple-resistant strains was never high and did not vary significantly during the investigation.

Patients.—In two of the six wards studied nasal swabs were taken from all patients on admission. In all, 1,138 patients were examined and *Staph. pyogenes* was isolated from 344 (30%). The majority (65%) of the carriers carried antibiotic-sensitive strains; 23% carried strains resistant to penicillin only; and strains resistant to penicillin and tetracycline were isolated from 12%. This last figure was unexpectedly high, but was partly accounted for by the fact that more than half the

TABLE VI

Date	No. Examined	No. of Carriers	Antibiotic Sensitivity of Strains		
			Percentage of Carriers		
			Pen. S.	Pen. R. Tet. S.	Pen. R. Tet. R.
October, 1957	446	211	23	69	8
March, 1958 ..	517	240	22	70	6
July, 1958	388	179	24	68	8
November, 1958	450	192	37	59	4
March, 1959 ..	480	235	35	61	4
July, 1959 ..	454	203	38	56	6

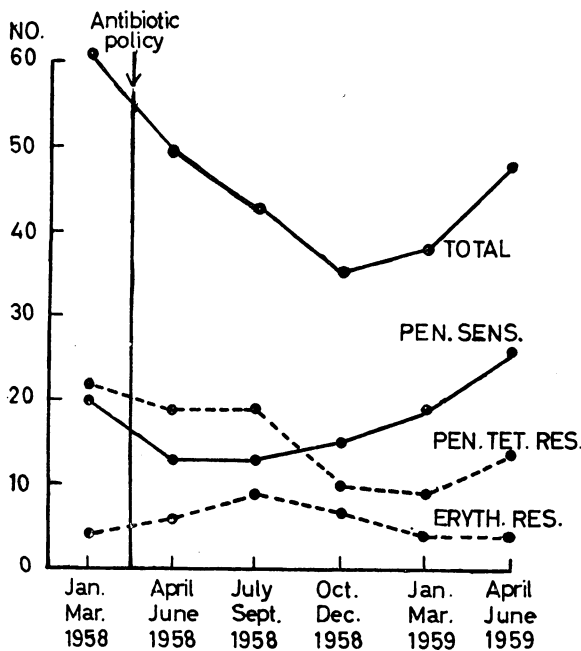


FIG. 3.—Number of strains of *Staph. pyogenes* with various antibiotic-sensitivity patterns.

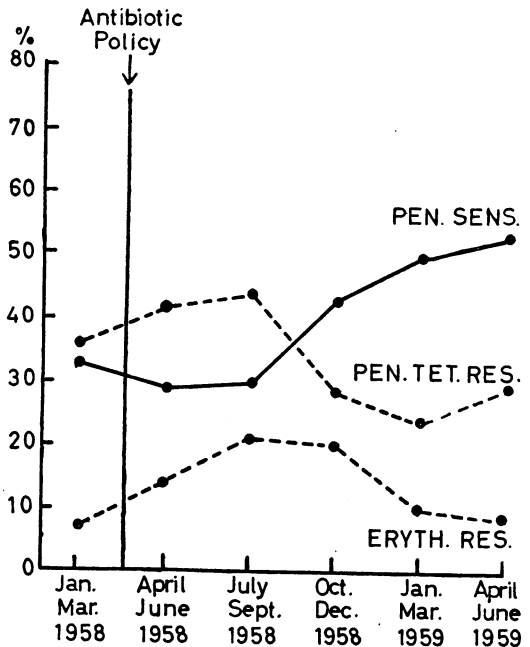


FIG. 4.—Percentage of strains of *Staph. pyogenes* with various antibiotic-sensitivity patterns.

patients who carried multiple-resistant *Staph. pyogenes* in the nose on admission had been transferred from other hospitals for treatment of renal failure.

With 530 patients nasal swabs were taken on admission and on one or more subsequent occasions. In most cases nasal carriage remained constant, but multiple-resistant strains which were isolated from 63 patients after a stay in hospital were not present on admission. Further analysis showed that 41 (12%) of 340 patients with negative swabs on admission picked up multiple-resistant strains, whereas this occurred with only 12 (7%) of 162 patients who on admission carried strains of *Staph. pyogenes* sensitive to all antibiotics or resistant to penicillin only.

Some form of staphylococcal sepsis developed in 116 patients from whom nasal swabs were examined. In 32 cases the strain isolated from the septic process was similar to that isolated from the nose on admission. In 16 cases both strains were antibiotic-sensitive; in 6 both were resistant to penicillin only; and in 10 both were resistant to penicillin and tetracycline. Nasal swabs were taken on more than one occasion from 43 patients who subsequently developed staphylococcal wound infection. As was found in a series recorded by Williams *et al.* (1959), the majority (22 out of 28) of those patients who were carriers at the time of infection had similar strains in nose and wound. But, since 15 of the 43 patients gave consistently negative nasal swabs, it cannot be assumed that nasal infection necessarily precedes or even accompanies wound infection.

Discussion

It is clear from this investigation that the ever-increasing incidence of drug-resistant staphylococcal infection in hospitals can be checked. In the hospital studied, until two years ago, the incidence of staphylococcal infection which was resistant to penicillin and tetracycline was steadily rising, and in October, 1957, the figure had reached 70%, whereas the incidence of infection sensitive to penicillin had fallen to 12%. A year after the introduction of the controlled antibiotic policy the figures were reversed and penicillin-sensitive staphylococcal infections in the hospital were more frequent than infections resistant to penicillin and tetracycline. It is possible that these results might have been even better were it not that with the transfer of patients for treatment on the artificial kidney we were continually being supplied with multiple-resistant staphylococcal infection from hospitals all over England.

To what extent these results are the direct effect of the antibiotic policy is difficult to determine. Undoubtedly the anti-cross-infection measures previously introduced played a part, and were probably responsible for the fall in the total incidence of staphylococcal infection per patient from 10% to 7% between January and July, 1958. The latter figure of 7% cannot be regarded with any satisfaction, but since it includes all forms of sepsis, both of wounds and of chest infections, however insignificant, it compares not unfavourably with the incidence of surgical cross-infection recorded by other workers (Howe, 1954; Jeffrey and Sklaroff, 1958; Shooter *et al.*, 1958).

Analysis, on the basis of bacteriophage typing, of the strains of *Staph. pyogenes* responsible for the infections shows a similar trend towards penicillin sensitivity, which suggests that the actual emergence of drug-resistant staphylococci in the hospital has been checked.

Moreover, in the last quarter of the investigation a few individual strains appear to have reverted from drug-resistance to drug-sensitivity. Thus two antibiotic-sensitive strains, of phage type 52A.80 and 83 respectively, were encountered in a ward where strains of similar phage type had previously been resistant to penicillin and tetracycline. Similarly, a strain of phage type 47.53.77 resistant to both these antibiotics appeared to give rise to a mutant sensitive to penicillin but resistant to tetracycline.

It seems likely that these findings are the result of the antibiotic policy, the two most important features of which were limitation in the use of penicillin and double chemotherapy. Reduction in the total amount of penicillin used in the hospital and its total abandonment in four of the six surgical wards probably favoured the natural tendency of penicillinase-producing staphylococci to give rise to penicillin-sensitive mutants. (Barber, 1949; Bondi *et al.*, 1953; Fairbrother *et al.*, 1954).

The introduction of universal double chemotherapy is a potentially dangerous policy, since it entails a considerable increase in the use of each antibiotic and makes it more difficult to keep any in reserve. In the present experiment the consumption of tetracycline antibiotics in the hospital went up; it seems almost certain, therefore, that the policy of always giving a second antibiotic was effective in preventing or at least delaying the emergence of tetracycline-resistant staphylococci. There are, however, other objections to an increase in the use of broad-spectrum antibiotics, and possibly this was one of the reasons for an increase in chest infection due to *Ps. pyocyanea* noted in the second winter of the trial.

Erythromycin and novobiocin were also used more freely than would otherwise have been the case. Staphylococci develop resistance very rapidly to both these antibiotics if administered separately, but so far the combination appears to have been effective in preventing the emergence of resistant strains. Combination of erythromycin with chloramphenicol did not prevent the development of drug-resistance. Though during the course of the investigation the incidence of staphylococci resistant to erythromycin did not significantly increase, unlike that of penicillin- and tetracycline-resistant strains it did not decrease, so that the proportion of multiple-resistant strains which are resistant to erythromycin has considerably risen.

Changes in the nasal carrier state of the nursing staff were less marked, but throughout the investigation it was apparent that the strains of *Staph. pyogenes* carried by the nurses were not the ones responsible for infections in patients. After the introduction of the antibiotic policy, however, there was a small increase in the percentage of nurse carriers who carried penicillin-sensitive strains.

At this stage it is pertinent to ask to what extent this experiment has been of practical value. Seeing that the total incidence of staphylococcal infection per patient remained stationary during the last year of the investigation, how important is the change in drug sensitivity? Provided new antibiotics continue to appear, does drug-resistance matter? In answer to this, evidence has been presented which indicates that some, at any rate, of the multiple-resistant strains of *Staph. pyogenes* in hospital have enhanced capacity both to initiate infection and to cause generalized disease.

It does not, of course, follow from this that drug-resistant strains are always of high virulence. Indeed, in *in vitro* experiments the reverse is usually the case. But in hospitals drug-resistant staphylococci have emerged as the result of the transfer of strains from patient to patient in the presence of antibiotics, and this form of animal passage has inevitably favoured the selection of highly virulent organisms. With the associated elimination of drug-sensitive strains the drug-resistant staphylococci have been left a relatively clear field.

If this is the case, attempts to reverse the process are of considerable importance; but, clearly, a controlled antibiotic policy gives us no respite from fighting cross-infection. Nevertheless, in view of the ubiquity of the staphylococcus and the consequent impossibility of eliminating all potentially pathogenic strains from the hospital environment, it seems reasonable to concentrate on those strains most likely to be dangerous. At present, in most hospitals these appear to be multiple-resistant organisms, usually of phage group III or type 80. It is possible that if we concentrate our attack on these strains we shall favour the selection, in hospitals, of less virulent staphylococci.

Summary

The incidence and drug-resistance of all staphylococcal infections in the surgical wards of a large general hospital have been studied over the period October 1, 1957, to June 30, 1959. In the six months prior to the investigation a number of anti-cross-infection measures were introduced into the hospital, and in April, 1958, a controlled antibiotic policy was put into operation.

During the investigation 5,239 patients were admitted to the wards studied and 452 had a staphylococcal infection. The total incidence per patient of all types of staphylococcal infection fell from 10% to 7% between January and July, 1958, and thereafter remained stationary.

At the beginning of the investigation 70% of the infections were resistant to penicillin and tetracycline and only 12% were sensitive to penicillin. At the end of the investigation 36% of the infections were resistant to penicillin and tetracycline and 48% were sensitive to penicillin. Analysis of the strains of *Staph. pyogenes* (on the basis of phage type) showed a similar trend towards penicillin sensitivity.

Most of the infections were localized and many were very slight, but 49 patients developed generalized infection and 24 of these died; 44 of the generalized infections and 23 of the fatal infections were due to multiple-resistant strains; 12 of these patients had been transferred from other hospitals for treatment of renal failure and were already infected on admission.

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OPEN LUNG BIOPSY FOR DIFFUSE PULMONARY LESIONS

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Diffuse pulmonary lesions have always presented a diagnostic challenge. In spite of intensive investigation, many cases remain obscure until further developments or even necropsy reveal their nature. Various methods have been devised to obtain a portion of lung tissue for histological, bacteriological, or chemical examination. Biopsy by means of a needle, drill, or thoracoscope appears to be inadequate. The only method of obtaining an adequate specimen which is both visibly and palpably diseased is open biopsy. This method was first described by Klassen *et al.* (1949), and further articles have appeared from other centres in the United States. So far no report on this subject has appeared in the British literature. We should therefore like to record the experience of this procedure at the London Chest Hospital during the past five years.

Method

General anaesthesia is employed in all cases. The site of the incision is planned according to the maximal radiological distribution of the disease. In earlier cases a routine thoracotomy incision was used with or without removing the rib. In later cases it was found that a smaller antero-lateral incision, usually about 6–8 in. (15–20 cm.) long, could be employed, with the possibility