types of condenser-humidifier. If the gauze element is sterilized it will be safe to reuse it from a bacteriological point of view, but the resistance to breathing will be increased and the humidifying power will be decreased so that in time it may need to be replaced on these grounds.

Summary and Conclusions

A theory has been developed to describe the performance of condenser-humidifiers in general and extended to cover more fully the type in which the patient breathes through a number of flat wire gauzes in series. An example of the "multiple-gauze" type, containing 10 gauzes, manufactured by Messrs. Garthur (London) Ltd., has also been tested experimentally; the results agreed with the theory.

Condenser-humidifiers can produce a substantial degree of humidification of inspired air in all normal circumstances by returning to the patient water vapour breathed out in expiration. They perform best when the fresh gas entering the humidifier from the room, or from a cylinder of compressed gas, is cold and damp

rather than hot and dry. If a patient with a tracheostomy or an endotracheal tube is breathing fairly moist cool room air a good condenser-humidifier can completely replace the humidifying properties of the upper respiratory tract.

The multiple-gauze type of condenser-humidifier appears to be the best design from a theoretical point of view and the 10 gauzes of the Garthur device give a performance close to the best possible for a condenser-humidifier. The device made by Drägerwerk with 15 gauzes should be marginally better.

We are indebted to Professor William W. Mushin for his continual interest and guidance throughout this work. We are also grateful to Messrs. Garthur (London) Ltd. for supplying the 10-gauze condenser-humidifier used in the experiments.

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ABOLITION OF STAPHYLOCOCCAL CROSS-INFECTION IN A THORACIC SURGICAL WARD

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Cross-infection due to *Staphylococcus pyogenes* is still common, and numerous suggestions have been made by different workers to combat it. It is clear from most of their reports that, although the cross-infection rate was reduced, complete eradication was not achieved. The idea of dealing with hospital cross-infection on an epidemiological basis by eliminating the nasal reservoir of staphylococci, using an antibiotic dust in the form of droplet nuclei, was first suggested by Elek and Fleming (1960a, 1960b). The same approach was used later by means of an individual antibiotic spray by Stratford, Rubbo, Christie, and Dixon (1960) and Barber and Warren (1962) with encouraging results. Individual spraying requires assiduous application and continuous vigilance. Our experience with the original method of Elek and Fleming shows that cross-infection can be eliminated by a very simple approach, and we would like to report our experience with methicillin spraying in a thoracic surgical ward, where the risk of cross-infection was especially high.

Past History of Infection in the Ward

This ward, standing on its own and connected with other wards by open corridors, had a high cross-infection rate in the past and was closed twice for this reason. During its first closure in 1958, when the cross-infection rate was 18%, the ward was modernized and the number of side wards was increased, with partitioning up to ceiling height.

The following preventive measures were introduced—some at the time of reopening, some later, when the cross-infection rate was rising again. (1) Broom-sweeping was discontinued and suction machines were introduced for ward-cleaning. (2) All blankets were replaced by open-weave broadloom cotton blankets, and were changed once a week on the beds of infected patients. Sheets were changed daily for these patients. The linen was carefully collected into closed bins and

no counting of linen took place in the ward. (3) All dressings were collected into paper bags and put into bins with self-closing lids. (4) The clinically infected cases were isolated in the side wards and barrier-nursed. Furthermore, when space permitted, this included patients with infected sputa. (5) Nasal swabs were taken regularly from nursing and medical staff, and those with even minor skin sepsis were excluded from duty. (6) As a nasal prophylaxis, "naseptin" was administered to all patients from the time of admission twice daily, under the supervision of the ward sisters. (7) Such antibiotics were given as were indicated by the results of the sensitivity tests on the infecting organisms.

In spite of all these measures, although the cross-infection rate was low for a time after the reopening of the ward, it slowly rose, culminating in a fatal case of staphylococcal septicaemia in April, 1960, which led to the second closure of the ward for 11 weeks. It was reopened again and once more the cross-infection rate gradually rose (the incidence of cross-infection before and after the second closure is shown in Figs. 1 and 2). It was at this time that the trial of methicillin spraying was begun in the middle of December, 1960.

Method

The spray, a "spraydex" window-cleaning bottle-and-spray, containing a solution of 10 g. of methicillin ("celbenin") in 200 ml. of tap-water was used. This solution was made up freshly each morning and was kept at 4° C. between use. At each use approximately 1.5 ml. of this solution was sprayed in the air above the bed of each patient and also in the treatment rooms. This procedure was carried out four times a day at four-hourly intervals.

In the first six months of the trial methicillin was also given parenterally to each patient operated on, beginning on the morning of operation and continuing for five days. The dosage was 1 g. four-hourly for two days

and 1 g. six-hourly for three days. No other antibiotics were given during this five-day period. During the second six months of the trial parenteral methicillin as a prophylactic antibiotic was discontinued.

Fig. 1.—Incidence of cross-infection before and after the trial.

Fig. 2.—Total percentage of cross-infected patients.

Laboratory Investigations.—Nasal swabs were taken from each patient on admission and thereafter once a week; a swab was also taken the day before operation. The same procedure applied to sputa. These materials were inoculated on blood-agar plates incubated aerobically for 48 hours. To cater for the possibility that there might be sufficient methicillin in the sputa to inhibit the growth of staphylococci inoculated with these specimens, a sensitive staphylococcus was streaked on a heavily inoculated part of each plate as a control. In no instance was there evidence of inhibition. All coagulase-positive staphylococci isolated were tested for sensitivity to methicillin and other commonly used antibiotics. Those found resistant to penicillin and tetracycline were also phage-typed.

Results

In the first six months of the trial there were two infected wounds that could be classified as cross-infection. One was an infected burn on the buttock, and occurred three weeks after the trial started. The other, an infected tracheostomy wound, occurred four weeks later. Both cleared up on treatment with methicillin. In the second six months there was not a single case of wound or sputum cross-infection (Fig. 1). Patients on admission carried a number of staphylococcal strains in their noses and sputa, but all these patients became clear within the first seven days (see Table).

During the 12 months of spraying no side-effects to methicillin were noted. There were no hypersensitivity

phenomena either in patients or in nursing staff. The parenteral injections of the drug were well tolerated, and, even without procaine, there were no complaints about painful injections. No strains of *Staph. pyogenes* naturally resistant to methicillin were encountered, nor did any resistant strains develop during the period of the trial.

Results of Laboratory Investigations

	On Admission		Acquired	Not Cleared in 7 Days
	Negative	Positive		
<i>Sputa</i>				
1960:				
July ..	10	1	2	3
August ..	19	1	5	6
September ..	19	1	3	4
October ..	16	1	7	8
November ..	15	2	2	4
Start of Trial				
December ..	11	3	1	1
1961:				
January ..	14	3	0	0
February ..	16	2	0	1
March ..	15	5	0	1
April ..	16	2	0	0
May ..	24	0	0	0
June ..	17	1	0	0
July ..	16	0	0	0
August ..	19	0	0	0
September ..	16	2	0	0
October ..	14	0	0	0
November ..	13	1	0	0
December ..	12	0	0	0
<i>Nasal Carriage</i>				
1960:				
December ..	11	3	2	1
1961:				
January ..	16	1	0	0
February ..	16	2	0	0
March ..	20	0	0	0
April ..	16	2	0	0
May ..	22	2	0	0
June ..	16	2	0	0
July ..	12	4	0	0
August ..	18	1	0	0
September ..	17	1	0	0
October ..	12	2	0	0
November ..	13	1	0	0
December ..	12	0	0	0

Discussion

Nasal carriage of staphylococci has for a long time been implicated as the major source of hospital cross-infection. To this may be added the dissemination of organisms from infected sputa. On a thoracic surgical ward, where active physiotherapy is carried out and the patients are encouraged to cough, this mode of spread must be of considerable importance. Before the start of the trial many of the methods recommended by various workers were tried, in particular naseptin, but without success. This was also the finding of Henderson and Williams (1961) based on a controlled trial. All the other measures advocated had similarly only a transient influence on the cross-infection. In marked contrast, however, was the effect of methicillin-spraying. Shortly after its use was begun in the face of the high cross-infection rate which had re-established itself four months after the reopening of the ward, the spraying produced a *permanent eradication* of both staphylococcal carriage and cross-infection. After the first three months of the trial period of one year, the only source from which staphylococci could be isolated from a patient who had been in the ward for one week or longer was a deep-seated infection already established in the patient before admission.

It appears that there is a cumulative effect of the antibiotic. During the first three months there were a few instances of patients with nasal or sputum carriage on admission who did not become clear within a week,

although the majority did so; after this time carriage never persisted beyond one week after admission. Furthermore, it was only during this initial three-months period that the two instances of apparent cross-infection were found. The burn on the buttock occurred three weeks after the trial started, when the environment presumably was not yet free of staphylococci. The second case, which occurred at the seventh week of the trial, was the infected tracheostomy. Though no staphylococci were isolated from the sputum of this patient on admission, the trap specimen taken when the tracheostomy was performed contained *Staph. pyogenes*. It is quite likely that the first sputum was not a representative sample of the bronchial flora. Both of these cases cleared up on treatment with methicillin.

It must be stressed that during the 12 months of the trial no infected case from whatever source was denied admission to the ward, and cases of staphylococcal empyema and lung abscesses were among those admitted. In the second six months of the trial these patients did not receive parenteral methicillin until after operation, which in some cases was some weeks after admission. In spite of the fact that some of these cases excreted staphylococci for a few weeks no cross-infection occurred. It seems likely that methicillin-spraying was effective in eliminating both nasal and sputum carriage of staphylococci, because an atmosphere was established which contained a sufficiently high concentration of minute particles of the drug. It is thought that the droplet nuclei remaining suspended in the air yielded particles small enough to penetrate the respiratory passages and so reach the staphylococci in their breeding-ground. The continuous build-up of the drug eliminated carriage and therefore the staphylococcal reservoirs in the ward. The cumulative effect appears to represent a build-up of the drug in the dust to an efficient level.

The result of this trial had a profound influence on the general attitude of the medical and nursing staff. Instead of expecting cross-infection they became confident that it would not occur. Staphylococcal cross-infection is notorious as a major cause of prolonged post-operative stay of patients in hospital. It was noticed that, until the newly gained confidence referred to above was established, the figures for the average post-operative stay of patients did not reflect the elimination of cross-infection. Prior to the trial and during its first six months it had been the custom to keep some of the patients in hospital a few days longer pending transfer to a convalescent home. It became apparent in the second six months of the trial that the interval between a patient becoming fit for discharge and the date of transfer to a convalescent home was widening. The policy then was adopted of discharging the patient home to await convalescence. The average post-operative stay between October, 1959, and November, 1960, excluding the three-months closure, was 23.8 days. In the first six months of the trial it was 23.7 days. In the second six months of the trial the average post-operative stay was 14.8 days.

One possible complication of methicillin-spraying could be the occurrence of hypersensitivity to methicillin. Cross-sensitivity between methicillin and penicillin G has been reported in the literature (Stewart, 1960, 1962). Inevitably during the trial some patients were admitted to the ward who were known to be hypersensitive to penicillin. These patients were kept under special surveillance for any reaction to methicillin, but none

was found. Nor did any of the other patients or the staff show any hypersensitivity phenomena.

Ulstrup and Ødegaard (1961) in a short trial also noted a reduction in nasal carriage, but their theory that this would reduce infections of infants after leaving hospital was not borne out.

At first sight there are many theoretical objections to the spraying of an antibiotic in clinical use. Existing naturally resistant strains of *Staph. pyogenes* (Jevons, 1961) may increase or fresh resistant strains may emerge. If either of these occurred quickly, the antibiotic might be deprived of much of its legitimate usefulness. In fact, in spite of extensive use of the drug over the course of a full year no resistant strains were found, and there is both theoretical and experimental evidence (Elek and White, 1963) suggesting that in the special case of methicillin this danger must not be exaggerated.

Cost of Applying the Method.—The most expensive part of the treatment was the use of parenteral methicillin (average £15 per patient). The parenteral use of methicillin, however, proved unnecessary after a brief initial period, as shown by the equally good results in the second six months of the trial. It has been estimated that the spraying of a ward of this size might cost about £14 a week. Against this has to be set the reduction of the post-operative stay of the patient. At the time of the trial the cost of keeping a patient in hospital was £5 a day.

Subsequent Experience.—Spraying was discontinued at the end of November, 1961, deliberately to test the effect. Unfortunately at the same time the surgical wards were reorganized and structural alterations were made to the operating-theatre. The ward originally used for spraying was no longer used for immediate post-operative cases, only new admissions and late post-operative cases being admitted. All immediate post-operative cases were taken to a ward which was divided into three sections with ten beds each and two cubicles for isolation. All the preventive measures detailed in Nos. 1 to 7, except the application of naseptin cream, were continued in both wards. In spite of this the sputum cross-infection rate rose to 15% in one and 12.5% in the other ward. The cross-infection rate of wounds amounted to an additional 12.5% in the sixth month after spraying.

Summary

Methicillin-spraying was instituted for one year in a thoracic surgical ward which had a bad history of staphylococcal cross-infection, requiring several closures. For the first six months patients also received pre- and post-operative methicillin systemically, but during the second half of the trial this was discontinued.

Although infected patients continued to be admitted to the ward as before, no instance of cross-infection occurred in any of 224 people admitted.

A genuine eradication of cross-infection was brought about by this procedure where other measures based on different principles failed. The method is based on building up and maintaining an atmosphere containing minute particles of methicillin which on inhalation produce sterilization of the reservoirs of *Staph. pyogenes*. When, as a result of this, the overall concentration of staphylococci falls below a critical level, cross-infection ceases.

Methicillin-spraying is not suggested as a general method of prevention of staphylococcal hospital cross-

infection, but only in situations of special risk, such as the thoracic unit described and where a sufficiently high cross-infection rate has been reported.

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EVOLUTION OF NATURAL RESISTANCE TO THE NEWER PENICILLINS

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The *raison d'être* of methicillin, and its continuing efficacy, are dependent on its virtual immunity to the hydrolytic action of penicillinase. Because of this, practically all strains of *Staphylococcus aureus* are sensitive to it; drug-resistance has not been reported during treatment; and, despite intensive screening and widespread use, very few naturally resistant strains have been reported (Jevons, 1961; Knox, 1961a; Barber and Waterworth, 1962). It has been known from the start, however, that *Staph. aureus* could be made resistant to methicillin in the laboratory (Rolinson *et al.*, 1960), though not always easily (Stewart, 1961; Barber and Waterworth, 1962). Such resistance, like that of the naturally resistant strains, is not associated with inactivation of the drug by penicillinase, and there is no evidence to date that any staphylococcus can form a specific methicillinase (Barber, 1961; Stewart, 1961). The situation is therefore different from that which obtained with penicillin G in its earlier days; nevertheless, fears have been expressed that the efficacy of methicillin will be ephemeral, and, indeed, the fate of all other antibiotics which joined battle with the staphylococcus would seem to justify such fears.

It is obvious that the usefulness of methicillin and its analogues in the future will depend upon the extent to which resistance emerges under clinical conditions. For this reason, when we began to use methicillin in 1959 we embarked at the same time upon a programme of assaying every staphylococcus isolated and reisolated from patients and staff against several derivatives of 6-aminopenicillanic acid to enable us to identify and

trace resistant strains if ever they occurred. The present report gives the results obtained to June 15, 1962.

Methods

In general, our methods were similar to those described in previous papers (Stewart, 1960, 1961), with special attention in the present study to the following.

Microbiology

All strains of *Staph. aureus* isolated from lesions, nasal carriers, etc., were screened in agar flood-inoculated plates against 10 mm. blotting-paper disks of penicillin, methicillin (10 µg.), and, successively, of various newer derivatives of 6-aminopenicillanic acid, in appropriate concentration. Organisms showing colonies or haloes in the inhibitory zone, or other indications of resistance, were titrated in liquid media to their end-points.

Test for Inactivation of Penicillins.—Three methods were used. (1) Broth containing the highest concentration of antibiotic permitting full overnight growth of any given staphylococcus was centrifuged at 3,000 r.p.m. (20 minutes). The supernatant was assayed against *Sarcina lutea* in parallel with control solutions of the particular penicillin left in sterile broth at 37° C. for the same period, and also of similar broth inoculated with non-resistant penicillinase-forming staphylococci. The percentage inactivation was calculated from semi-log dose-response lines, constructed anew for each series of tests. (2) Whole-cell sediments from the broth residues of method 1 were added for two hours at 37° C. to standard solutions of the penicillins, which were then assayed similarly against *S. lutea*, with similar controls. (3) A two-stage membrane technique was developed by modifying our earlier method (Stewart *et al.*, 1961; Holt and Stewart, 1963). Staphylococci were inoculated on marked spots on broth-soaked cellulose-acetate membranes (Oxoid) placed on agar containing the particular penicillin in a concentration calculated to permit growth of the test organism on the overlying membrane and thereby act as an enzyme inducer, but to inhibit completely the indicator organism (Oxford staphylococcus or *S. lutea*). The membrane was inspected after overnight incubation on the drug-loaded agar to check that full growth had occurred. It was then removed and the agar flooded with 0.2 ml. suspension (standardized at about 10⁸ organisms per ml.) of indicator organism. The plate was then reincubated for 18–24 hours. Destruction of the particular penicillin by diffusible enzyme was shown by growth of the indicator organism below the marked spots of active staphylococci and positive controls (excess of cereus 5B penicillinase).

Clinical

Our practice is to examine nasal swabs from patients and staff in the wards for acute cases at monthly intervals, or more often according to circumstances. The first methicillin-resistant *Staph. aureus* was detected in the course of this routine procedure. The phage-type and antibiotic sensitivity pattern of this organism were determined and thereafter a continuous check was maintained upon this patient and her contacts by repeated swabbings in this ward, and by exposing plates in various situations. When the resistant strain appeared in another ward the same intensified procedure was applied until eventually its incidence in the wards at large was determined. In parallel with this, records were kept of