Summary

Twenty-one patients with ventricular septal defect have been treated by open surgery using extracorporeal circulation.

The clinical features, indications for operation, surgical technique, and post-operative care are presented.

The results of surgical treatment are given and the implications of these are discussed.

We are indebted to Dr. R. E. Bonham-Carter, not only for referring many of these patients, but also for his continued encouragement and support; to Dr. J. D. James and Dr. P. B. Booth and the staff of the North London Blood Transfusion Service for their unfailing co-operation; to Professor J. V. Dacie and his colleagues in the department of haematology in the Postgraduate Medical School of London; and to the matron and nursing staff of Hammersmith Hospital. To Mr. J. R. Robson, Mr. E. Gains, Miss M. Murphy, and Mrs. E. Victor, the technical staff of the department of surgery, and to Mr. C. Lordon and the staff of the workshops of the Postgraduate Medical School we owe a special debt of gratitude.

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Natural Causes, a new play on a challenging theme by Mrs. Vera Colebrook, was given a number of performances in London last month at the Hovenden Theatre Club. The action of the play takes place in the country house of an old lady who has just suffered a cerebral haemorrhage, complicated by the onset of pneumonia. Her family doctor had previously given her a solemn promise that should she fall seriously ill he will not administer any antibiotic or other drug that may prolong her life—or, rather, “prolong her death.” On the insistence of her daughter-in-law, a well-known London consultant is called in; he advises injections of penicillin. The family doctor refuses to give these, telling the consultant of his promise and insisting that there is all the difference in the world between administering a lethal dose and withholding a life-saving drug. The old lady's two children want their mother to die as she had lived, with dignity and without fear of mental deterioration. But her shrewish daughter-in-law desires only that her mother-in-law's life might be prolonged for the sake of the benefits her annuity brings to the family. The Hovenden Players, directed by Miss Valery Hovenden, were completely successful in bringing out the realism of this situation. A philosophical nurse—who assumes a more pronounced Irish brogue with private cases, because “it goes down so lovely with the patients”—adds a touch of humour to the play, which is not concerned with “mercy killing” but rather with the truth or otherwise of Clough's “Thou shalt not kill, but needst not strive officiously to keep alive.” The whole vexed problem, while remaining unsolved, is given an unexpected twist by the London consultant at the end of the play.

STAPHYLOCOCCAL INFECTION RESISTANT TO CHLORAMPHENICOL, ERYTHROMYCIN, AND NOVOBIOCIN

EFFECT OF ANTIBIOTIC COMBINATIONS ON THE EMERGENCE OF RESISTANT STRAINS

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Control of the use of antibiotics in hospital communities is imperative if we are to combat the adaptability of the staphylococcus to these agents. Until recently most hospitals in Great Britain have tried to keep erythromycin and novobiocin in reserve, to be used only for the treatment of staphylococcal infection resistant to all other antibiotics. By 1957, however, about 50% of all staphylococcal infection occurring in many hospitals was found to be resistant to penicillin, streptomycin, and tetracycline, so that erythromycin and novobiocin inevitably had to be used more extensively.

The danger of the increased use of these two drugs is obvious, since it is well recognized that staphylococci develop resistance to erythromycin and novobiocin more readily than to any other antibiotic except streptomycin (cf. Hobson, 1954; Garrod and Waterworth, 1956; Lin and Coriell, 1957). Moreover, this change occurs quite often during the treatment of staphylococcal infections with erythromycin (Thomson *et al.*, 1956) and novobiocin (Nichols and Finland, 1956), and the spread of erythromycin-resistant strains in a hospital where the use of this antibiotic is extensive may be very rapid (Lepper *et al.*, 1954).

In an attempt to combat this situation a policy for the control of antibiotics was introduced into this hospital at the beginning of April, 1958. The essential items of the policy were: firstly, abandonment of penicillin except in certain wards of the hospital, and, secondly, the use of two antibiotics in combination wherever possible and always when erythromycin or novobiocin was used.

About six months previously a cross-infection committee was appointed to investigate staphylococcal infection in the hospital and to introduce measures for its control. The effect of these measures and that of the antibiotic policy are inextricably confused. Nevertheless analysis of the antibiotic sensitivity pattern of all staphylococcal infections in the hospital throughout the year has brought to light certain facts about the emergence of erythromycin- and chloramphenicol-resistant strains which are considered worth reporting.

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Bacteriological Methods

All staphylococcal infections in the wards of the hospital between October 1, 1957, and September 30, 1958, were studied bacteriologically. The period covered thus included six months before the introduction of the antibiotic policy and the first six months of its operation. The strains of *Staph. pyogenes* isolated were tested for sensitivity to penicillin, streptomycin, tetracycline, chloramphenicol, erythromycin, and novobiocin by the ditch-plate method. The concentration of antibiotics used in the ditch was: penicillin, 10 units per ml.; streptomycin, 50 or 200 g. per ml.; chloramphenicol, 50 g. per ml.; and tetracycline, erythromycin, and novobiocin 25 g. per ml. The Oxford staphylococcus was streaked across the centre of each plate as a control.

Strains were recorded as sensitive if they showed a degree of sensitivity similar to that of the Oxford staphylococcus, resistant if they grew up to or across the ditch, and partially resistant if there was an intermediate degree of inhibition. Representative strains were also tested by a serial dilution method in broth. The latter tests showed that strains recorded as partially resistant were often only two to four times less sensitive than the standard organism, but strains recorded as resistant always showed a more than eightfold difference.

Most of the strains on first isolation and those showing a change in sensitivity pattern were phage-typed by the method of Williams and Rippon (1952) using 21 phages.

Antibiotic Administration

After the introduction of the antibiotic policy in April, 1958, the use of drug combinations caused an increase in the consumption of most of the antistaphylococcal antibiotics except penicillin. The approximate changes were as follows: Penicillin, $\div 3.2$; tetracycline, $\times 1.4$; chloramphenicol, $\times 1.6$; erythromycin, $\times 2$; novobiocin, $\times >5$.

In the six months following the introduction of the antibiotic policy 284 patients were treated with chloramphenicol, 275 with erythromycin, and 170 with novobiocin. The most frequently used combinations were erythromycin and novobiocin (108 patients) and erythromycin and chloramphenicol (69 patients). Further details of the use of these three antibiotics are given in Table I. Similar figures are not available for the period before the antibiotic policy.

TABLE I.—Number of Patients Treated with Chloramphenicol, Erythromycin, and Novobiocin, April 1–September 30, 1958

	Total	In Combination with				Alone*
		Chlor.	E yth.	Novo.	Other Antibs.	
Chloramphenicol	284	—	69	8	70	137
Erythromycin ..	275	69	—	108	45	53
Novobiocin ..	170	8	108	—	25	29

* Or in combination with a sulphonamide preparation.

Analysis of Sensitivity Patterns

A total of 982 staphylococcal infections were present in the hospital during the year. Antibiotic sensitivity has been analysed separately for each quarter, and the results are presented in the Chart. The total numbers of staphylococcal infections in each quarter were respectively 247, 245, 270, and 220.

It will be seen that the incidence of infection resistant to penicillin fell from 80% at the beginning of the year to 60% at the end. This is associated with a corresponding fall in the incidence of tetracycline-resistant infections (from 55% to 27%), practically all of which were also resistant to penicillin and which were in most instances the result of cross-infection in the hospital. The percentage of infections resistant to penicillin and sensitive to tetracycline rose slightly in the second quarter and thereafter remained steady.

In the first quarter of the year the incidence of staphylococcal infection resistant to penicillin and tetracycline was 46 per 1,000 admissions to the hospital. The cross-infection committee appointed at the beginning of the investigation recommended a number of measures for the control of cross-infection which were put into operation throughout the year. Probably as a result of these, although seasonal influences cannot be excluded, the corresponding figures for the remaining three quarters of the year were respectively 33, 32.7, and 20. The fall in the percentage of staphylococcal infections in the hospital that were resistant to penicillin and tetracycline is almost certainly a reflection of this. It is probably too early for the antibiotic policy introduced in the middle of the investigation to have had much effect on the incidence of penicillin-resistant infection.

Percentage of staphylococcal infections resistant to various antibiotics, October, 1957, to September 30, 1958. A=Penicillin. B=Tetracycline. C=Penicillin resistant and tetracycline sensitive. D=Erythromycin. E=Chloramphenicol. F=Novobiocin.

The percentage of infections resistant to chloramphenicol, erythromycin, and novobiocin remained low throughout the year. Since, however, nearly all these infections were also resistant to penicillin, streptomycin, and tetracycline, their importance cannot be exaggerated. The figures for erythromycin in each quarter were respectively 4.8, 2.8, 4.0, and 6.4, and the significance of the slight rise in the last quarter is increased by the accompanying fall in the incidence of multiple resistant infection as a whole.

Chloramphenicol-resistant Infection

The incidence and source of chloramphenicol-resistant infection are summarized in Table II. In the whole year there were 30 infections resistant to this antibiotic, and on

TABLE II.—Chloramphenicol-resistant Infections

	Total No. of Infections	No. of Strains of <i>Staph. pyogenes</i>	No. of Strains also Resistant to Erythromycin
Oct. 1 to March 31	14	11	4
April 1 to Sept. 30	16	12	4
	30	23	8

Source of Chloramphenicol-resistant Strains

Isolated from patients on admission ..	3	1
Chloramphenicol-sensitive strain developed resistance to chloramphenicol during treatment with:		
Chloramphenicol and erythromycin ..	5	2
Erythromycin alone ..	1	1
First strain isolated from patients who had been treated with:		
Chloramphenicol alone or plus tetracycline ..	2	1
Chloramphenicol plus erythromycin ..	3	1
Erythromycin plus tetracycline ..	1	1
Other strains ..	8	1
	23	8

All strains were resistant to penicillin, streptomycin, and tetracycline except those isolated on admission. All strains were sensitive to novobiocin and vancomycin.

the basis of bacteriophage typing it was shown that the 30 infections were probably caused by 23 strains of *Staph. pyogenes*. Three of the strains showed partial resistance and 20 were recorded as resistant. It will be seen that there is no significant difference in the figures before and after introduction of the new antibiotic policy.

Of the 23 strains involved, three were isolated from patients on admission. The remaining 20 were all resistant to penicillin, streptomycin, and tetracycline, as well as to chloramphenicol, and seven, together with one strain isolated on admission, were also resistant to erythromycin. In six instances strains of the same phage-type were isolated on two occasions from the same patient, the first being chloramphenicol-sensitive and the second chloramphenicol-resistant, and three of these strains developed resistance to erythromycin at the same time. Five of the six patients from whom these strains were isolated had been treated with chloramphenicol and erythromycin, and one with erythromycin but not chloramphenicol.

In 14 cases the only staphylococcus isolated was chloramphenicol-resistant. Five of the patients from whom these strains were isolated had previously had chloramphenicol and one erythromycin. The remaining eight strains were isolated from patients who gave no history of recent antibiotic treatment.

Erythromycin-resistant Infection

Table III summarizes the information in relation to erythromycin-resistant infection. In the whole year 23 strains of *Staph. pyogenes* resistant to this antibiotic were responsible for 44 infections. In the first half of the year eight strains caused 19 infections, whereas in the first six

TABLE III.—Erythromycin-resistant Infections

	Total No. of Infections	No. of Strains of <i>Staph. pyogenes</i>	No. of Strains also Resistant to Chlorampheni- col
Oct. 1 to Mar. 31 ..	19	8	4
April 1 to Sept. 30 ..	25	15	4
	44	23	8
<i>Source of Erythromycin-resistant Strains</i>			
Isolated from patients on admission ..		3	1
Erythromycin-sensitive strains developed resistance to erythromycin during treatment with:			
Erythromycin alone or plus tetracycline ..		3	1
Erythromycin plus chloramphenicol ..		4	2
First strain isolated from patients who had been treated with:			
Erythromycin alone or plus tetracycline ..		3	1
Erythromycin plus chloramphenicol ..		4	1
Chloramphenicol without erythromycin ..		3	1
Other strains ..		3	1
		23	8

All strains were resistant to penicillin, streptomycin, and tetracycline except those isolated on admission. All strains were sensitive to novobiocin and vancomycin.

months of the antibiotic policy 15 strains caused 25 infections. Two of the 23 erythromycin-resistant strains were recorded as partially resistant and 21 as resistant. It was noted, however, that many strains which were resistant on primary isolation became less resistant after subculture in the laboratory. Thirteen of the strains were tested against spiramycin: three were as sensitive as the Oxford staphylococcus, four showed a twofold, and six a fourfold increase in resistance to this antibiotic.

Three of the strains were present in patients on admission. The remaining 20 were all resistant to penicillin, streptomycin, and tetracycline, as well as to erythromycin, and eight were also resistant to chloramphenicol. In seven cases erythromycin-sensitive and erythromycin-resistant strains of the same phage-type were isolated consecutively from the same patient, and three of the strains showed a corresponding increase in resistance to chloramphenicol.

All seven patients had been treated with erythromycin—four in combination with chloramphenicol and three alone or in combination with tetracycline, to which the initial strain was not sensitive.

In 13 instances the only strain of *Staph. pyogenes* isolated was erythromycin-resistant. Ten of the patients concerned had previously had antibiotic treatment: three with erythromycin alone or plus tetracycline; four with erythromycin and chloramphenicol; and three with chloramphenicol but not erythromycin. The remaining three strains were isolated from patients who had not had recent treatment with antibiotics.

TABLE IV.—Novobiocin-resistant Infections

	Total No. of Infections	No. of Strains of <i>Staph. pyogenes</i>
Oct. 1 to March 31 ..	2	2
April 1 to Sept. 30 ..	7	2
	9	4
<i>Source of Novobiocin-resistant Strains</i>		
Novobiocin-sensitive strain developed resistance to novobiocin during treatment with:		
Novobiocin alone ..		1
Novobiocin plus erythromycin ..		2
Other strains ..		1
		4

Three strains were resistant to penicillin, streptomycin, and tetracycline; and sensitive to chloramphenicol, erythromycin, and vancomycin. One strain was sensitive to penicillin, streptomycin, tetracycline, chloramphenicol, erythromycin, and vancomycin.

Novobiocin-resistant Infection

Throughout the year only four strains of *Staph. pyogenes* resistant to novobiocin were isolated (see Table IV), two in each half. Three of the strains were each isolated from only one infection. The fourth strain was responsible for infections in four children and two nurses in the same ward.

Three of the strains were also resistant to penicillin, streptomycin, and tetracycline, and sensitive to chloramphenicol, erythromycin, and vancomycin. One strain which developed resistance during novobiocin treatment was sensitive to all other antibiotics tested. The source of the strain which caused six infections is completely unknown. The remaining three strains all developed resistance during treatment with novobiocin, in two cases given in combination with erythromycin and in one case given alone.

Association of Chloramphenicol and Erythromycin Resistance

A number of observations in this study indicate an association between chloramphenicol and erythromycin resistance. Thus eight of the erythromycin-resistant strains were isolated from patients who had previously had erythromycin and chloramphenicol. In no instance, on the other hand, was an erythromycin-resistant staphylococcus isolated from a patient treated with erythromycin and novobiocin, in spite of the fact that after the introduction of the antibiotic policy 108 patients were treated with the latter combination and only 69 with erythromycin and chloramphenicol.

No fewer than 8 of the 23 erythromycin-resistant strains also showed resistance to chloramphenicol. In three cases strains of the same phage-type were isolated on two occasions from the same patient, the first being sensitive to both these antibiotics, and the second resistant. Two of the patients concerned had been treated with chloramphenicol and erythromycin, and one with erythromycin only. Three other strains showing this double resistance came from patients who had recently had antibiotic treatment, one with both the antibiotics concerned, one with erythromycin, and one with chloramphenicol.

With two strains, both of which were responsible for small outbreaks of infection (reported elsewhere; cf. Barber and Dutton, 1958), the resistance to chloramphenicol was inconstant. Thus strains resistant to penicillin, tetracycline, and erythromycin of a single phage-type infected several patients in one ward, and some of the cultures isolated were grossly resistant to chloramphenicol, whereas others were as sensitive as the Oxford staphylococcus. In one case the initial patient had been treated with erythromycin only, and in the other the patient had had a number of antibiotics, including chloramphenicol, but had never had erythromycin.

It seems probable from these observations that there is some cross-resistance between erythromycin and chloramphenicol, and preliminary studies *in vitro* have shown this to be the case. The investigation will be published in full elsewhere (Csillag and Barber), but it has already been found that strains of *Staph. pyogenes* rendered resistant to erythromycin by passage in this antibiotic develop a moderate and sometimes transitory increase in resistance to chloramphenicol.

Discussion

This investigation emphasizes the danger of erythromycin-resistant infection becoming a hospital problem if the unrestricted use of erythromycin is permitted. Since there is evidence of cross-resistance between erythromycin and chloramphenicol, combined treatment with these two antibiotics offers no solution. Monnier and Schoenbach (1951) and Fusillo, Romansky, and Kuhns (1953) demonstrated a similar increase in resistance to chloramphenicol when staphylococci were passaged in the presence of tetracycline compounds. A study of cross-resistance with chloramphenicol and other antibiotics is now in progress.

Combined treatment with erythromycin and novobiocin seems more promising. Lowbury (1957) showed that the combination of these two antibiotics delayed the emergence of erythromycin-resistant staphylococci *in vitro* and *in vivo*. In the investigation here recorded no erythromycin-resistant staphylococci were isolated from 108 patients treated in this way. This number is, of course, small, and it is too early to say whether this combination will do more than postpone the evil day; but even this is of value, since it might tide us over until new antibiotics were available.

Scott and Waterworth (1958) treated 110 patients suffering from boils with a seven-day course of erythromycin (55 patients) or E 129 (55 patients) and found no instance of increased bacterial resistance to either antibiotic. Coagulase-positive staphylococci were, however, isolated from only 15 of the original boils after treatment, although a further 23 strains, which were isolated from fresh lesions developing during or after treatment, were also found to be erythromycin-sensitive.

The *British Medical Journal* (1958) asked whether the determining factor in the development of resistance to erythromycin was "the nature of the lesion, dosage, or duration of treatment, or a property of the staphylococcus itself." In the present series length of treatment was not necessarily prolonged, and some of the patients had been treated with erythromycin for only a few days before the appearance of erythromycin-resistant staphylococci. With regard to the lesions, however, although one strain came from a boil treated with erythromycin alone, most of the strains came from more severe infections such as pneumonia, lung abscess, peritonitis, or post-operative sepsis.

The type of staphylococcus concerned is probably of considerable importance. In the present series nearly all the strains showed multiple resistance to antibiotics, and it has been suggested that such strains may be highly mutagenic (Treffers *et al.*, 1954; Barber and Dutton, 1958). All the erythromycin-resistant strains were also shown to belong to phage groups III except for a few strains of type 80. It has been shown that group III staphylococci yield antibiotic-resistant variants more readily than do other strains (Barber and Whitehead, 1949; Rountree and

Thomson, 1949; Barbour and Edwards, 1953), and the same may well be true of phage-type 80 staphylococci, which have recently become a hospital menace (Rountree and Freeman, 1955; Anderson and Williams, 1956; Gillespie and Alder, 1957; Duthie, 1957).

While staphylococci of such virulence and adaptability continue to circulate in hospital communities it is important that the use of erythromycin should remain under strict control. Although novobiocin, vancomycin, ristocetin, and kanamycin have been added to our antistaphylococcal armoury, the last three have serious toxic effects, particularly on the eighth nerve. Since novobiocin, like erythromycin, has the defect that staphylococci readily become resistant to it, both should be used sparingly, and neither except in combination with each other or another chemotherapeutic agent.

Summary

A policy whereby antistaphylococcal antibiotics were used only in combination was introduced into a large general hospital.

The antibiotic sensitivity of all strains of *Staph. pyogenes* isolated from infections in the hospital was studied during a period lasting six months before the introduction of this policy and six months afterwards.

Analysis of erythromycin- and chloramphenicol-resistant infection has shown evidence of cross-resistance between these two antibiotics. Of 23 erythromycin-resistant strains, 11 came from patients who had been treated with chloramphenicol (in eight cases in combination with erythromycin and in three cases without). Moreover, eight of the erythromycin-resistant strains also showed resistance to chloramphenicol, although in two cases the patient had been treated with erythromycin but not chloramphenicol.

No such cross-resistance was noted between erythromycin and novobiocin, and of 108 patients treated with this combination none yielded a staphylococcus resistant to erythromycin, although in two instances strains resistant to novobiocin were isolated.

It is a pleasure to thank the many clinical colleagues who co-operated in this investigation and, in particular, Dr. Peter Elmes, without whose energy and enthusiasm the work would not have been possible. Our thanks are also due to Eli Lilly and Company for free supplies of erythromycin ("ilotycin").

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