AUREOMYCIN AND ERYTHROMYCIN THERAPY FOR STR. PYOGENES IN BURNS

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In an earlier report (Jackson, Lowbury, and Topley, 1951), aureomycin and oxytetracycline (" terramycin "), given by mouth, were shown to be effective in eliminating *Streptococcus pyogenes* from burns. Oral aureomycin has since then been our routine treatment for such infection ; the organisms have nearly always been absent from swabs taken five or seven days after treatment was started, and usually have not reappeared later.

Occasionally burns were not cleared of *Str. pyogenes* by such treatment, and the streptococci isolated have been found moderately resistant to aureomycin and oxytetracycline ; all of them, however, were sensitive to penicillin and also to erythromycin. Penicillin applied locally is valuable as a prophylactic agent, and for this reason has been adopted as a routine application for burns (Jackson *et al.*, 1951). In established streptococcal infection of burns, however, its value as a therapeutic agent is limited, probably because of penicillinase-producing organisms in the same burn (Cruickshank, Squire, and Topley, 1948 ; Jackson *et al.*, 1951). Erythromycin seemed to us the most suitable alternative for the treatment of infections with streptococci resistant to aureomycin and oxytetracycline. Previous work (Heilman *et al.*, 1952 ; Haight and Finland, 1952) has shown the value of erythromycin against *Str. pyogenes* both *in vitro* and in throat infections.

We have therefore made a trial, in which oral aureomycin and erythromycin were compared in the treatment of burns infected with *Str. pyogenes* sensitive to both antibiotics. We also describe in this paper the clinical value of chemotherapy for *Str. pyogenes* as shown by the effect of aureomycin treatment on the result of grafting operations.

Comparison of Aureomycin and Erythromycin

Conduct of Trial.—During a period of eight months oral aureomycin or erythromycin was given for six days to patients over 1 year of age on the appearance of streptococci of Lancefield's group A (*Str. pyogenes*) on any burn. Cases were admitted alternately to the erythromycin and the aureomycin treatment groups. Separate lists were kept for patients treated by the exposed and by the covered methods. A few patients with aureomycin-resistant streptococci on their burns were treated with erythromycin but not included in the controlled trial.

Dosage.—For patients over 6 years of age the dosage was 600 mg. of erythromycin or 1 g. of aureomycin daily ; those under 6 years of age were given 400 mg. of erythromycin or 500 mg. of aureomycin daily, usually as a suspension. A few patients were given a slightly lower daily dosage of erythromycin (400 mg. for adults and 300 mg. for children). Erythromycin was given as " ilotycin " tablets and paediatric preparation, and occasionally as " erythrocin " tablets. In a few cases the course of treatment was prolonged beyond the sixth day for clinical reasons. In some of the cases treated with aureomycin the course was curtailed to four days on account of vomiting and diarrhoea.

Bacteriology.—Swabs taken from burns at all dressings and operations, and daily from those treated by the exposed method, were examined by the methods previously described (Jackson *et al.*, 1951). Haemolytic colonies were subcultured and grouped by Lancefield's method. A proportion of the group A streptococci were typed at the Oxford Public Health Laboratory. All strains of *Str. pyogenes* were tested for sensitivity to erythromycin, aureomycin, oxytetracycline, and penicillin by a tube diffusion test (Hurst, 1954), and a proportion were also tested by a tube dilution test. The sensitivity to these agents of *Staphylococcus aureus* from all burns in the ward was also tested, so that the emergence and spread of resistant variants could be detected.

Results of Trial.—Table I shows that all the burns in the trial were free from *Str. pyogenes* after three or more days' treatment with erythromycin or aureomycin. A slightly larger proportion of burns in the erythromycin than in the aureomycin series did not show *Str. pyogenes* during the first three days of treatment. Reappearance of streptococci on burns from which the organisms had been cleared was infrequent (3 out of 24 in the erythromycin, 5 out of 24 in the aureomycin series). All of seven burns (on five patients) from which aureomycin-resistant streptococci had been isolated were free from streptococci after a course of treatment with erythromycin. Two of these patients had had previous treatment with aureomycin, at the end of which streptococci were still found in the burns. The value of erythromycin is inferred from the results of this trial by the fact that it was as effective as aureomycin, which had been found effective in a previous trial (Jackson *et al.*, 1951). We used a dosage of erythromycin smaller than that commonly recommended—for example, Haight and Finland (1952). No toxic effects were noted in the patients receiving erythromycin.

TABLE I.—*Comparison of Erythromycin and Aureomycin Therapy for Burns Colonized with Str. pyogenes*

	Burns of Patients Treated with			
	Erythromycin		Aureomycin	
	Streptococci Present	Streptococci Absent	Streptococci Present	Streptococci Absent
At end of course, or after 3 days' treatment ..	0	24 (100%)	0	24 (100%)
During first 3 days of course ..	4	13 (76%)	6	7 (54%)

Note.—In each series there were 24 burns in 21 patients.

Sensitivity of Str. pyogenes to the Antibiotics

With the exception of the seven aureomycin-resistant strains mentioned above, all the streptococci isolated from patients in the trial were sensitive to aureomycin and oxytetracycline (minimal inhibitory concentration 0.4–0.8 μg. per ml.), and to erythromycin (minimal inhibitory concentration 0.5 μg. per ml.).

Streptococci resistant both to aureomycin and to oxytetracycline have been isolated from burns in this unit on three occasions during the past year. On the first and third occasions they appeared in the burns of one patient only and did not spread to others in the same ward. In each case the patient was being treated with aureomycin for an infection with aureomycin-sensitive streptococci, but the organisms were found to persist after treatment and to have become resistant to aureomycin and to oxytetracycline. The strains of *Str. pyogenes* isolated from these two cases were of types 3 and 9 respectively, and it was found that in each case the serological type was the same in the sensitive strain isolated before aureomycin therapy and in the resistant strain isolated after. It seemed most likely, therefore that in these cases resistant variants had emerged on burns during

the course of aureomycin therapy. On the second occasion when aureomycin-resistant streptococci appeared, they were of type 9 and spread from a patient treated with aureomycin to four other patients in the same ward who were not receiving the antibiotic.

No aureomycin- and oxytetracycline-resistant streptococci were found in the nose or throat of any patient or member of the staff on any of these occasions. All strains of *Staph. aureus* isolated during the trial were sensitive to erythromycin. Since then erythromycin-resistant staphylococci have appeared on the burns of several patients, most of whom were at the time having a course of erythromycin therapy. Further details about these organisms will be reported elsewhere.

The minimal inhibitory concentration of oxytetracycline and of aureomycin towards the resistant streptococci was 12.5 μg. per ml. On subculture of the tubes showing inhibition to large volumes of broth, growth of a sensitive strain was obtained from aureomycin concentrations up to 25 μg. per ml. and from oxytetracycline concentrations up to 400 μg. per ml.; resistant streptococci were obtained from aureomycin concentrations up to 50 μg. per ml. and from oxytetracycline concentrations up to 200 μg. per ml. By these tests sensitive and resistant streptococci appeared to have the same low sensitivity to the bactericidal action of aureomycin and oxytetracycline.

Attempts to induce resistance to oxytetracycline by subculture through increasing concentrations of the antibiotic were unsuccessful with 10 streptococci, including a sensitive type 9 organism isolated from a burn on which resistant streptococci appeared later.

Clinical Value of Therapy for Str. pyogenes in Burns

The importance of *Str. pyogenes* as a pathogen in burns is widely recognized, and an association between its incidence and the failure of skin grafts, delayed healing, and other adverse effects has been noted (Bodenham, 1943; Clarkson and Lawrie, 1946; Jackson *et al.*, 1951). The association of adverse results with a higher incidence of a particular organism is, however, inadequate evidence of its pathogenicity.

The pathogenic action of *Str. pyogenes* on burns, suggested by the results of a prophylactic trial of penicillin (Jackson *et al.*, 1951), receives further support from the grafting results in a series of burns cleared of *Str. pyogenes* by aureomycin, and a collateral series in which aureomycin was not given or was started less than three days before the grafting operation. The patients in this comparison (not a controlled trial) were comparable in respect of age, sex, and area of burn. Table II shows that in 11 out of 44 (25%) burns of patients treated with aureomycin skin-grafting operations failed (< 80% "take"), compared with 16 out of 18 (89%) failures in burns of patients to whom no aureomycin was given before the operation ($\chi^2 = 18.8$; $P < 0.001$). A high proportion of failures (7/9, or 78%) was found also in burns colonized by *Str. pyogenes* when treatment with aureomycin was started less than three days before the operation. It seems most likely that these results are related to the presence or absence of *Str. pyogenes* at the time of operation.

TABLE II.—*Aureomycin Therapy for Burns with Str. pyogenes and Results of Subsequent Skin-grafting*

Treatment	Results of Skin-grafting				*Str. pyogenes* in Burn 1–7 Days after Operation		
	80% or More "Take" (Success)	Less than 80% "Take" (Failure)	Total	% Failures	Present	Total	% Present
Aureomycin started 3 days or more before operation	33	11	44	25	4	40	10
(*a*) Course stopped before operation	12	5	17	29	3	15	20
(*b*) Course continued after operation	21	6	27	22	1	25	4
Aureomycin started less than 3 days before operation	2	7	9	78	4	9	44
No aureomycin given before operation	2	16	18	89	11	18	61

Interference by *Str. pyogenes* with skin-grafting and healing of deep burns makes it important to eliminate this organism by chemotherapy when it breaks through the prophylactic barrier of penicillin. For this purpose oral aureomycin and erythromycin are both very effective, the latter having been effective also on three occasions when aureomycin-resistant streptococci emerged during treatment with aureomycin.

It is desirable that erythromycin should not be used when other antibiotics are equally effective, in order to prevent (or at least delay) the emergence of erythromycin-resistant staphylococci. We would advocate the use of erythromycin for the treatment of streptococcal infection of burns in severely ill patients whose recovery might be jeopardized by the toxic side-effects commonly found during aureomycin therapy; but in such patients frequent examination of the burns and nares for staphylococci resistant to erythromycin is advisable.

Summary

A comparison of oral erythromycin and oral aureomycin therapy for elimination of *Str. pyogenes* from burns has shown that the former antibiotic is as effective as the latter.

Streptococci resistant to aureomycin and oxytetracycline occasionally emerged during treatment with aureomycin, but retained their sensitivity to erythromycin and penicillin and were eliminated from burns during a course of treatment with erythromycin.

The clinical value of chemotherapy for *Str. pyogenes* is demonstrated in the case of aureomycin by improved results of skin-grafting operations, provided therapy begins at least three days before the operation.

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Co-operation between parents and the local health authority is a vital factor in helping mentally deficient children who live at home, said Miss PATRICIA HORNSBY-SMITH, M.P., Parliamentary Secretary to the Ministry of Health, in opening a new occupation centre at Mansfield on October 6. Family life was as valuable to the mentally handicapped as it was to others, she continued, and the public was alive to the need for a good all-round domiciliary service. At the beginning of this year there were 244 occupation and training centres for mental defectives, compared with 180 in 1939 and only 100 in 1948. The number receiving training at the centres was well over 9,000, and some 1,600 were receiving training in their own homes. The provision of facilities was a major problem for local authorities, especially in rural areas. Miss Hornsby-Smith paid tribute to the excellent work being done by the National Association of Parents of Backward Children.